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FACTORS IN FUNCTIONAL RECOVERY FOLLOWING SECTION OF THE OCULOMOTOR NERVE IN MONKEYS

BY

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Introduction

THE downward rotation of the eye-ball in primates is normally associated with a corresponding movement of the upper eyelid. After oculomotor nerve paralysis, however, the superior eyelid which formerly drooped may not descend ; indeed, this eyelid may actually move up while the globe and the lid on the normal side move down. Such disjunctive movements were described in man by Gowers (1879), who attributed the absence of associated lid movements to immobility of the globe in the vertical plane. Fuchs (1893) thought the phenomenon due to spreading of impulses in the nucleus of the oculomotor nerve, and Bielschowsky (1935) suggested as the cause indiscriminate regeneration of the axis cylinders in the reunited oculomotor nerve—an explanation similar to that of Lipschitz (1906) for the abnormal movements of facial muscles in patients recovered from Bell's palsy. Ford and Woodhall (1938) have recently used similar reasoning to explain various disorders of motility and sensibility which appear in the course of regeneration of cranial, spinal and autonomic nerves in man.

Similar abnormal movements of eyelid and eye-ball have been reproduced experimentally in a chimpanzee (Bender and Fulton, 1938) and all the evidence pointed to misdirected regeneration as the cause of the dissociated palpebral

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and ocular movements. The present communication deals with corresponding experiments carried out in monkeys. In all monkeys studied, some recovery of nerve function occurred after section of the third nerve.

Procedure

The observations have been made on a series of 15 young rhesus macaques (*M. mulatta*) and one chimpanzee, in which either the oculomotor, trochlear, or both nerves were severed aseptically under amytal anæsthesia, usually with scissors ; the cut ends generally became separated from one another by 2–3 mm. To secure adequate exposure a large bone flap was necessary. The dura was then incised and freely turned back so that the hemisphere could be retracted without damage to the temporal lobe. A similar exposure was made for the trochlear nerve. In a number of instances proof of regeneration was obtained by secondary resection of the regenerated nerve. Daily observations were made during the first weeks after operation.

Experimental Results

Section of oculomotor nerve.—Intracranial section of the third cranial nerve in these animals resulted in the typical ophthalmoplegia seen in man and chimpanzee, i.e. there was complete ptosis, external deviation of the eye, and maximal dilatation of the pupil. The pupil did not constrict on any form of stimulation. The only orbital movement was in a horizontal plane between the outer canthus and vertical meridian. Generally by the 5th to 7th post-operative day the ptosis and external deviation of the eye-ball lessened. A change in tone in the levator palpebræ could be seen at this time, and the " fright reaction " as described by Bender (1938) had begun to be detectable. About this period also, contractions in the levator palpebræ could be reproduced by parenteral injection of eserine and acetylcholine. In other words, after the period allowed for the nerve-endings to degenerate, the denervated levator palpebræ muscle began to show signs of sensitization to acetylcholine.

The ptosis continued to diminish and by the 25th or 28th post-operative day the palpebral fissure was more than three-quarters open ; when the monkey looked down with the normal eye, the upper lid of the affected eye failed to move in unison. Indeed, neither the lid nor the globe on the affected side ever moved in conjunction with vertical (up and down) excursions of the normal eye. This failure of the lid to descend has been termed by ophthalmologists the " pseudo-Graefe sign " to differentiate it from the lid lag observed in exophthalmic goitre, known as the " Graefe sign."

In Experiment 1, which was typical, improvement was progressive so that by the 32nd day after operation the monkey was able to adduct the affected eye slightly past the vertical meridian. On the 34th day ptosis had disappeared completely. On the 30th day not only did the lid fail to descend but actually moved upward in association with downward gaze in the sound eye. This movement of the lid appeared to be due to a contraction of the levator palpebræ. The upward movement in the lid was also noted when the monkey looked to

the side requiring the action of the fully recovered internal rectus muscle, i.e. on the 49th day. There were abnormal contractions also in the recovered internal rectus muscle. When the monkey looked down with the good eye, the affected eye turned nasally. Slight adduction was again observed when the monkey looked upward. In other words, the recovered levator palpebræ and internal rectus muscle contracted simultaneously in association with intended vertical or internal movements.

Vertical movements in the recovered eye were never encountered. This, however, did not mean that the elevators or depressors of the globe remained paralysed ; on the contrary, the absence of upward or downward movements was due to simultaneous contraction in the elevators and depressors of the eye which gave no resultant movement. When, in the eye recovering from an ophthalmoplegia, the inferior rectus muscle had been previously cut, upward movements of the globe became apparent ; that is, as soon as one of the antagonists was eliminated, the action of the other became evident.

Signs of regeneration of pupillary constrictor fibres appeared later ; the first indication was on the 49th day (decrease in the pupillary diameter). At 60 days slight constriction of the pupil in association with the lid closure reflex was evident. On the 90th day there was slight constriction in association with fixation at a near point, and after many months reaction to direct and indirect stimuli appeared. In one instance the pupil constricted when the animal looked to the side requiring the action of the internal rectus muscle. This was the only instance of participation of the pupil in the massive contraction following regeneration of the oculomotor nerve. The excursions of pupillary constrictor responses were always small. All contractions were augmented by previous eserinization. The foregoing data illustrate that, whenever any one of the muscles supplied by the regenerated oculomotor nerve contracted, the rest of the recovered muscles acted simultaneously.

Further evidence that the contractions *en masse* were associated with the regenerative process was brought out in stimulation experiments ; thus faradic stimulation of the cortical eye-fields, which would produce horizontal movement in the direction requiring the action of the recovered internal rectus, was accompanied by a definite retraction of the recovered upper eyelid ; similarly, stimulation of the reunited nerve proximal to the point of section 180 days after the original section resulted in a retraction of the upper eyelid, internal rotation of the globe, and slight constriction of the pupil ; stimulation distal to the point of section produced similar but more pronounced effects. Finally, section of the reunited nerve 145 days after the primary section caused a prompt reappearance of the ophthalmoplegia and abolition of responses in this eye to electric stimulation of the cortical eye-fields (Bender and Fulton, 1938). The course of regeneration in the oculomotor nerve was not materially affected by section or stimulation of the cervical sympathetic, trigeminal, or trochlear nerves.

Cervical sympathetic.—Stimulation of the cervical sympathetic trunk after section of the oculomotor nerve caused the usual exophthalmos with secondary separation of the eyelids, pilo-erection and enlargement of the pupil,

provided the pupil was not already maximally dilated. Cutting of the cervical sympathetic trunk or its superior ganglion was followed by enophthalmos, with secondary elevation of the lower lid edge and slight drooping of the upper lid (pseudo-ptosis). Although the dilated pupil in the ophthalmoplegic eye did not become smaller immediately, section of the cervical sympathetic in these monkeys caused the diameter of the pupil to decrease in a shorter time than in those in which only the oculomotor nerve had been cut. The pupil, after sympathetic denervation, dilated with intravenous or intramuscular injections of adrenaline (the phenomenon of adrenaline sensitization). The pupil, however, did not constrict with intravenous injection of solutions of eserine followed by acetylcholine. Eserine in the conjunctival sac constricted the denervated pupil as much as the normal pupil. Acetylcholine applied locally to either eye caused no response.

The fright reaction was somewhat augmented by resection of the cervical sympathetic trunk or the superior cervical ganglion, a point first noted by Mahoney and Sheehan (1936). The pseudo-Graefe phenomenon and ocular synkinesias appeared after the same interval irrespective of whether the oculomotor and cervical sympathetic nerves were severed simultaneously or seriatim.

Trigeminal nerve.—Simultaneous section of the third and fifth cranial nerves resulted in the usual oculomotor ophthalmoplegia, deviation of the jaw to the ipsilateral side, corneal areflexia, and facial anæsthesia (one animal). The pupil was maximally dilated despite the fact that part of its sympathetic supply via the fifth nerve had been interrupted. Recovery of oculomotor nerve function was not altered in this animal. The ptosis began to decrease on the usual day, the fright reaction was elicited as effectively as in monkeys with only the oculomotor nerve sectioned, and the pseudo-Graefe sign appeared in the 5th post-operative week. Movements of the jaw did not cause any abnormal movements in the eye or its lid.

Trochlear nerve.—In a monkey in which the oculomotor nerve had been sectioned previously and in which some recovery of function had occurred, stimulation of the trochlear nerve caused a distinct nasal and downward rotation of the globe over an arc of 2·0 mm. The rotation of the globe was visible during the movement of the blood-vessels on the bulbar conjunctiva. When the third and fourth cranial nerves were sectioned at one operation, recovery in power of the muscles supplied by the oculomotor nerve was not interfered with. The palpebral fissure began to open after the 6th day and the fright reaction appeared on the 7th post-operative day. The fright reaction, however, differed from that observed in other monkeys, since not only did the drooped eyelid elevate after fright, but the eye-ball moved slightly downward, presumably due to contraction of the denervated trochlearis muscle. The pseudo-Graefe phenomenon appeared at the usual time. Contraction in the levator muscle was always accompanied by a contraction in the internal rectus.

Incomplete section of oculomotor nerve.—The foregoing data indicate that ocular structures following recovery from a complete oculomotor nerve section tend to function *en masse*, individual actions of these muscles being permanently lost. When the oculomotor nerve was only partially cut, for example on its

superior surface, there followed a typical oculomotor ophthalmoplegia, and recovery occurred rapidly and completely save for the pupillary reflexes, which remained sluggish. There was no synkinesias in the lid or eye-ball and no contractions *en masse*. Individual actions of the recovered muscles were present and normal. Further studies of this phase of regeneration could not be carried out on the oculomotor nerve because this nerve or its branches is too inaccessible. For this purpose it was much easier to experiment with the facial nerve.

Facial nerve.—Complete transection of the facial nerve resulted, after time had been allowed for regeneration, in mass movements of all the recovered facial muscles. An incomplete lesion, on the other hand, i.e. a partial or hemisection, resulted in paresis of all the facial muscles, but recovery was rapid and complete. Except in localized areas (and this depended upon which fibres were originally cut) there were no simultaneous massive contractions. Contractions occurred in focal areas and appeared to be true synkenesias. These focal movements occurred whenever the normally innervated muscles supplied by the same but uncut part of the nerve were actively innervated. On the other hand, no synkinesia was noted in these normal muscles when the recovered muscles contracted.

Complete section of the third or seventh cranial nerves resulted in complete paralysis with loss of tone in the ocular and facial muscles. After a period allowed for nerve endings to degenerate, however, these muscles began to regain their tone. Thus 5 or 6 days after the oculomotor nerve was sectioned, a period corresponding with the time necessary for nerve endings to degenerate, ptosis of the upper eyelid began to diminish. The receding ptosis was due primarily to increase in muscle tone of the levator palpebræ. It was not due to activity of Mueller's palpebral muscle, since previous section of the cervical sympathetic trunk did not materially alter the rate of recovery from the ptosis. Similarly the paralysed facial muscles also regained their tone. This recovery in muscle tone could not be due to regenerating nerve fibres, for it appeared even after large blocks of nerve tissue had been resected. More significant, however, was the fact that the increased tone ran closely parallel to progressive increase in sensitivity of denervated muscle to acetylcholine (Bender, 1938).

Sensitivity of denervated muscles to acetylcholine.—The sensitivity of denervated muscles to acetylcholine is well recognized, but few quantitative determinations are available concerning the degree of this sensitivity on the intact animal—certainly no determinations have heretofore been reported in primate forms. Using monkeys with sectioned facial nerves, the denervated muscles were maximally sensitive 4–5 weeks after the nerve section.

Parallel to this increased sensitivity of the denervated muscle to acetylcholine was increased response of these muscles during fright ; the fright reaction was also augmented by eserine. After signs of nerve regeneration had manifested themselves (muscle twitches appearing as part of the reflex response), the sensitivity to acetylcholine began to decrease. In other words, as soon as the muscle was influenced by the regenerating nerve, it began to lose its sensitivity to such chemical agents as acetylcholine. The diminution of sensitivity during

funtional recovery of the muscle was gradual, extending over a period of several weeks.

Discussion

To account for the mass contractions which follow regeneration of the oculomotor nerve, one must consider the anatomical and functional changes which may accompany regeneration in a single oculomotor neuron unit.

(1) *The cell body*.—Fuchs (1893) thought that the pseudo-Graefe phenomenon was due to spread of impulses in the oculomotor nerve nucleus, i.e. to impulses arriving at non-functioning cells might jump to adjacent active cells. Thus it is conceivable that retrograde degeneration may cause physiological or anatomical changes in the ganglion cell, and that when regeneration of the axon has occurred the metabolism of the cell body may still be upset. Such a theory, however, would not account for the parallel observations on patients with regenerated sensory nerves in which stimulation of one point caused sensation in many points (Ford and Woodhall, 1938). This obviously could not be due to retrograde changes in the centre, or to alterations in the sense organs. Stopford (1926) explained the diffuse and perverse sensations felt after regeneration of sensory nerves on the basis of misdirection of nerve fibres.

(2) *The nerve scar*.—Langley and Anderson (1904), Kilvington (1905), Ramón y Cajal (1928), Howe, Tower, and Duel (1937) proved that during the process of repair the newly formed axis cylinders branch freely and grow indiscriminately into the distal stump, losing their former anatomical arrangements in new plexuses. In such circumstances an impulse intended for one group of muscle fibres may be shunted at the scar to other muscle masses, and the affected neurons when activated may thus cause widespread contraction. Whether all muscles contract to an equal degree depends upon the number of nerve fibres regenerated and how extensively the axis cylinders dichotomize. Examples of such partial contraction in the extra-ocular muscles have been observed in man (Bielschowsky, 1935 ; Ford and Woodhall, 1938). The ptosed eyelid may, for example, move up on attempted downward gaze, or *vice versa*, a phenomenon also explicable on the basis of misdirection. In the monkey it would appear that all muscles supplied by the cut oculomotor generally regain a share of the newly formed axis cylinders. The changes at the nerve scar may fully account for diffusion of impulses ; the normal topography of the nerve trunk may, however, be a contributing factor ; thus Compton (1917), Langley and Hashimoto (1917), and McKinley (1921) have all found internal plexuses within the normal peripheral nerve. Such an arrangement would predispose the regenerating axis cylinders to functional confusion.

These considerations also provide rational explanation of the signs observed in incomplete nerve sections, since a lesion affecting a few fibres in the main trunk would cause local misdirection at the scar.

(3) *The motor end-plate and muscles*.—Degeneration of the nerve endings causes the denervated muscles to become sensitive and contract readily in the

presence of chemical agents such as acetylcholine. After nerve regeneration, however, although the sensitivity of reinnervated muscle to acetylcholine diminishes, there may remain a functional abnormality such as heightened excitability, whereby any impulse reaching the recovered desensitized muscle would result in a contraction. This might account for the well-known persistent contractures observed in patients with Bell's palsy. When tonic impulses reach the facial muscles these altered muscles respond excessively, especially during phasic innervation, when the altered facial muscles contract *en masse*. Denny-Brown and Pennybacker (1938) have studied the post-paralytic facial contracture electromyographically. These records revealed rapid action currents of uniform size and shape. The outbursts which occurred at irregular intervals were of increased frequency following attempted innervation of muscle. Since the bouts of rapid discharge were periodic, they inferred that a focus in the nerve fibre or the motor neuron in the facial nucleus were intensely excited at intervals. Their findings suggested a central origin for the post-paralytic facial contracture.

Signs of acetylcholine sensitization of paretic muscles were, as already indicated, readily demonstrated following nerve section, and the phenomenon no doubt has an important bearing upon the course of functional recovery, especially before functional reinnervation appears. Unless the peripheral ramifications of the autonomic nervous system form a syncitium (Stöhr, 1927), the muscle tone which appears soon after denervation cannot be due to active innervation from other nerves. Resection of all local nerves, avulsion of large blocks of nerve tissue, and repeated section of possibly regenerated nerves do not diminish the resting tone of the affected muscles (Bender and Kennard, 1938).

Not only is there a restoration of a postural tone, but spontaneous electrical activity and fibrillations have been noted in these denervated muscles (Denny-Brown and Pennybacker, 1938). The spontaneous electrical activity was found to be enhanced by eserine (Rosenblueth and Luco, 1938). Tremors or fibrillations in the denervated muscles were also augmented by eserine (personal observations). Evidently, therefore, a chemical agent influencing these muscles must be responsible for the spontaneous activity and contracture. This substance might be related to acetylcholine and found in the body tissues and circulation.

In the foregoing analysis of changes in the motor neuron and muscle, the hypothesis of misdirection of regenerated axis cylinders seems best to explain the abnormal movements in the recovered muscles. The other two factors, that is, disturbances in the cell nucleus and in the denervated muscle fibres, may operate to some extent. It is doubtful whether cortical centres have any direct influence on the abnormal mass movements. General anæsthesia or cortical ablation of the facial or ocular centres do not abolish the movements *en masse*. Long after nerve regeneration is complete, abnormal mass movements persist. Some authors state that the abnormal mass movements can be made to disappear by re-education. In man, as related to the cranial and sensory nerves (Head, 1920), no amount of re-education yields return of

individual function. Sometimes in peripheral motor lesions re-education of a formerly paralysed part occurs, but chiefly through supplementary or trick movements (Pollock and Davis, 1933).

Summary

1. Recovery from intracranial section of the oculomotor nerve in monkeys is characterized by mass movements in all of the muscles supplied by the nerve.

2. The recovery in function of these muscles is not materially affected by section of the fourth or fifth cranial nerves, nor by extirpation of the cervical sympathetic chain.

3. Recovery and the phenomena attendant upon it are most likely due to arborization and misdirection of the regenerated axis cylinders.

4. It is suggested that the early appearance and continual increase in muscle tone which runs closely parallel to the increasing sensitivity of the denervated muscles to acetylcholine is due to a circulating chemical agent similar to acetylcholine in its action.

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FAMILIAL PRESENILE DEMENTIA

REPORT OF CASE WITH CLINICAL AND PATHOLOGICAL FEATURES OF ALZHEIMER'S DISEASE

BY

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ALTHOUGH it has been suggested that Alzheimer's disease is not uncommon (Malamud and Lowenberg, 1929 ; Mayer-Gross, 1938), cases which show a family history of presenile dementia are distinctly rare. Lowenberg and Waggoner (1934) have described such an example coming under observation at the age of 32, and reference was made in a discussion on presenile dementia between the sections of Neurology and Psychiatry of the Royal Society of Medicine in 1933 to "data suggestive of senile and presenile types of dementia in the direct ancestry of a number of patients" (Gillespie *et al.*, 1933). Lowenberg has also noted the occurrence of senile dementia in a father and Alzheimer's disease in the son.

In discussing the literature of familial and hereditary Alzheimer's disease, Lowenberg and Waggoner refer to a probable example in a father and daughter recorded by Schottky and to its occurrence in twins as reported by Braunmühl.

The present case is recorded as showing a family history of presenile dementia and a typical clinical course with histo-pathological findings of the disease which bears Alzheimer's name.

Case Record

L. T. J. E., a male aged 51 years, was admitted to hospital on 21st October, 1935, on account of mental deterioration and stiffness of the limbs. The following history was obtained from his wife. He was employed as a clerk in a Metropolitan Gas Company, where, being exceptionally good at figures, he held a post of considerable responsibility in the Accountant's Department. At the outbreak of the Great War he was given a similar post at Woolwich with the rank of major, and, his work having been of a consistently high standard, he was rewarded with a decoration. After the war he first returned to his former occupation, but soon ventured into a partnership with a friend in a motor engineering concern in which he took charge of the office and secretarial department. The business flourished and he had no reason to regret the change.

The present illness appears to have dated from 1929 or 1930, when the patient was 46 years of age. The first feature to be noticed was a blunting of his usual enthusiasm for various activities and a lack of interest in his ordinary pursuits. As he was assisted in his work by an efficient clerk whom he had himself trained, any falling away in his management of the business was, at first, not noticed. Towards the end of 1930 his friends were making allowances for his gross mistakes at bridge, a game at which he had formerly shown considerable skill. During the following years mental deterioration progressed, especially during the six months prior to his admission to hospital, so that a nurse had to be employed to help in his management. A year before his coming to hospital, however, he was still able, unaccompanied, to meet a friend at the railway station, but was not at this time displaying any interest in everyday occurrences.

His wife finds difficulty in estimating the time of appearance of the stiffness in his limbs. There is no doubt that immediately preceding the onset of mental failure he was playing a good game of tennis, and the earliest signs of loss of interest were accompanied by rapid and undue fatigability at this game. About a year later he noticed on holiday that he was finding it difficult to climb stiles. His movements gradually and progressively became less easily performed.

Mental State on Admission.—The most striking defect was in the intellectual field. There was profuse memory disturbance affecting remote but more particularly recent events. He was disorientated for time and place and was unable to give any account of himself. In a general way he appreciated simple questions, but only after an interval of time, and frequently the question had to be repeated. He exhibited paraphasia and perseveration. If he attempted a sentence of more than about six words, an unintelligible jargon usually resulted. Sometimes he recognized the fact that he had used the wrong word and occasionally after an effort, he was able to correct his mistake ; for example, when asked his name he replied, " Annie, Annie—no " (pause) " Louise " ; when asked his occupation he replied " coke, coke " (pause) " clerk." He named the year of his birth correctly, but could not state his birthday beyond " 11th—11th—11th." He named correctly such objects as a key, pencil, watch, penny, and sixpence ; a simple pocket-torch, however, he called (after much effort) a " microscope " ; a halfpenny he described as " ten shilling—no—no—one tenth " ; a fountain pen elicited " fountain, fountain—something." With his eyes closed he was unable to identify by their shape, size, and consistency any of the objects named above. He could read aloud some of the headlines in newspapers and magazines correctly but slowly. At times he made simple calculations on paper accurately, but at others he made gross errors. He was unable to name the days of the week, the months of the year, or the letters of the alphabet. He was disinclined to write owing to the difficulty resulting from spasticity, but on one occasion, when requested, he determinedly started to write " Friday," but could not proceed beyond the first letter. He was co-operative, but tired easily and had to have frequent rests during the examinations.

Physical Condition.—He showed general spasticity of the limbs, the arms

being held slightly flexed at the forearms and pronated ; there was definite resistance to passive movements ; the legs were similarly spastic and slightly flexed at the knees. In walking, progression was slow, with short steps, the knees slightly bent and the back bowed. No Parkinsonian mask was present and the movements of the neck were moderately free.

The pupils were average in size, equal, and reacted normally ; fundus oculi was natural. Facial movements were good ; tongue was slightly tremulous. Speech was hesitant, slurred, and incoherent, with sentences incompleted. Arm reflexes were brisk and equal ; abdominal reflexes could not be elicited. Knee-jerks were brisk and equal ; ankle jerks were sluggish ; plantar reflexes were indefinite, but mainly flexor. There was incontinence of urine and fæces. Sensation, as far as it was possible to judge, was intact, certainly as regards grosser forms. Cardio-vascular system was normal ; blood pressure was 120/75. Arteries were in good condition. Urine—nil abnormal was detected.

Subsequent Progress.—There was little change in the main features of the patient's condition during the first few weeks. His mood consistently suggested that he was worried and anxious. Occasionally he made spontaneous remarks of quite surprising quality, such as, " I've got very slow, I know " ; and on another occasion, when he almost tripped in walking, " I am a clumsy fool." At times he was irritable and threw the nearest suitable article. His habits were degraded unless careful attention was given to him. There was nothing to suggest that he was experiencing hallucinations. He also exhibited shocklike contractions of the legs and arms sufficient to spill water when holding a tumbler which was but three parts full.

During the following weeks he became rapidly worse. He was exceedingly restless and sleepless unless under the influence of sedatives. He continued to lose weight and became bed-ridden. Finally he developed difficulty in swallowing and was drowsy for a few days before his death on 18th December, 1935.

Family History

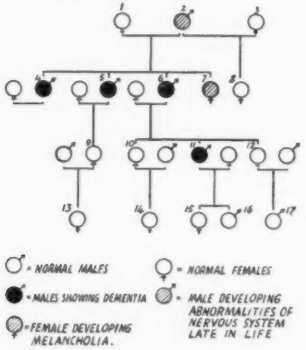
The accompanying diagram shows the family history as far as it can be ascertained. For the sake of convenience each member is numbered. The patient, L. T. J. E., is number 11.

His paternal grandfather (2) married twice, the first wife (1) being a first cousin. She died while still young and no abnormal features were noted. There were three sons and one daughter by this marriage. He afterwards married again, his second wife (3) living to the age of 90, and it is reported of her that she was always healthy. One daughter (8) resulted from this union. The grandfather (2) died at the age of 80 years. He is described as having been a clever, eccentric, and neurotic type, with insomnia. During the last two years of his life he developed twitching of the tongue and drooping of the eyelids. Unfortunately, no further information can be obtained, and it is not known if there was mental deterioration.

The four children of the first marriage are numbered (4), (5), (6), and (7). The eldest (4), a son, was a brilliant science student, who obtained a D.Sc.

degree. He went to Australia and became a Government analyst. About the age of 56, he developed loss of memory and mental deterioration which continued until his death at the age of 60. His letters to his relatives in this country showed well the extent and progress of his mental failure. There is no record of paralysis or spasticity. The second son (5) showed signs of mental

FAMILY HISTORY


= NORMAL MALES
= NORMAL FEMALES
= MALES SHOWING DEMENTIA
= MALE DEVELOPING ABNORMALITIES OF NERVOUS SYSTEM LATE IN LIFE
= FEMALE DEVELOPING MELANCHOLIA.

failure about the age of 63 years. He was admitted into Tooting Bec Mental Hospital in July 1922 at the age of 65. We are indebted to Dr. F. M. Turnbull for allowing us to see the case notes ; these showed that the patient, on admission, displayed considerable memory defect for recent events and was unable to think or speak coherently ; he was disorientated in time and place, and required assistance in dressing ; his habits were degraded. He gradually became more demented and died in April 1924, at the age of 67. There was no record of spasticity or paralysis. The third son (6) was the father of our patient. He was employed as an accountant in the same firm as that in which our patient subsequently held a post and was considered a trusted and gifted employee. At the age of 50 he began to show mental failure, and during the following two years this change became so pronounced that he was retired from active employment. For sentimental reasons he was allowed to remain in the office in an inferior position when he was long past usefulness. At the age of 53 he accidentally cut himself, developed septicæmia, and died. There is no record of difficulty in walking or speaking. The fourth sibling, a daughter (7), developed melancholia at the age of 45 years, and was admitted into Bethlem Royal Hospital in March 1902. We are indebted to Dr. J. G. Porter-Phillips for a description of this illness. It was the first attack, and when examined, she was in a state of severe depression and showed considerable anxiety. Although there was no retardation there was much inhibition of activity and she was unable to occupy herself in any way, except to talk about her misfortunes. She was actively suicidal and made one attempt to injure herself. She improved steadily and continuously until she was discharged " relieved " in February 1903. We are informed by the relatives that recovery was complete and she lived until about 65 years of age. She became very depressed again

shortly before her death. There is no certain evidence of mental deterioration in this case.

The daughter (8) of the grandfather's second marriage lived to be more than 80 years of age, and no abnormal features are reported.

In the next generation (9), (10), and (12) are reported to be healthy subjects ; (11) is our patient.

In the following generation the children are too young to be expected to show any example of the disease. The children (15) and (16) of our patient are described as being sensitive, somewhat neurotic, and inclined to be depressive in temperament.

In brief, therefore, it would seem that of the four children of the first affected generation, the eldest developed an intense dementia, beginning at 56 and proving fatal at 60. The second developed mental failure at the age of 63 and the illness progressed rapidly into a profound dementia with death from this cause at the age of 67. The third exhibited mental deterioration at the age of 50, but the progress of the disease was curtailed by a fatal septicæmia occurring two years later. These three were all males. The fourth sibling was a female who developed an involutional melancholia which resolved completely without mental deterioration, only to relapse again shortly before her death at the age of 65.

Post-mortem Examination

An autopsy was performed at Peckham House Mental Hospital and the brain was preserved intact for future study. No abnormal finding was reported at post-mortem examination beyond some atheroma of the aorta.

Brain (after fixation).—The brain weighed 1,470 gm. On examination it was symmetrical and there was no suggestion of wasting of the convolutions, although there was slight thickening of the leptomeninges, particularly over the frontal lobes. On stripping off the pia-arachnoid, however, there was seen to be slight but very definite shrinkage of the convolutions of both frontal lobes. The basal vessels were normal in size and distribution, and they appeared to be free from atheroma. On horizontal serial sectioning, the white matter of the cerebral hemispheres was firm in consistency and without any foci of softening. The grey matter, both of the cortex and basal ganglia, appeared normal. The lateral ventricles showed a slight degree of dilatation and the choroid plexuses were cystic. The left cerebral hemisphere weighed 570 and the right 550 gm. The pons, cerebellum, and medulla appeared normal to naked eye examination.

Histology.—The histological findings in the brain are those which we normally associate with Alzheimer's disease, namely, extensive changes of a degenerative nature in the nerve cells and the presence of abundant senile plaques. The accompanying photographs demonstrate the intensity of the disease and the reactive processes at work.

The alterations are widespread in the cortical grey matter and are most marked, as is usual in Alzheimer's encephalopathy, in the cornu Ammonis and frontal cortex : in these areas the normal architecture has been destroyed, all

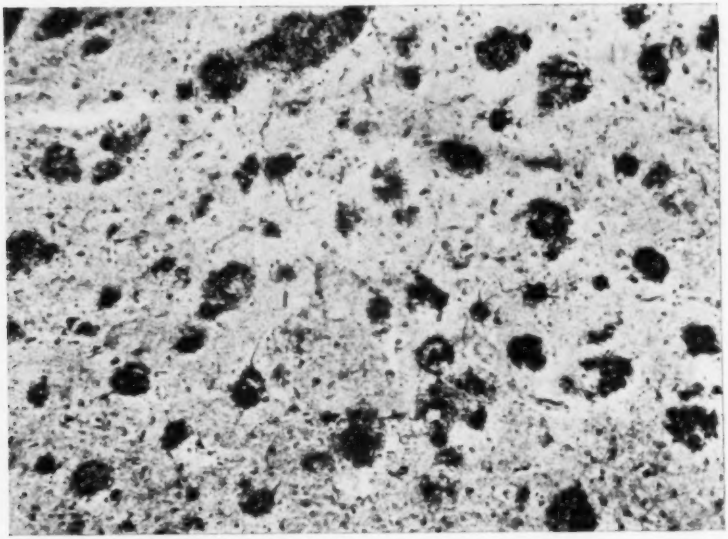


Fig. 1.—*Frontal Cortex :* showing abundance of senile plaques ; microglial processes can be distinguished projecting from some of these, especially the smaller of them. (Hortega's microglial method ; low power.)

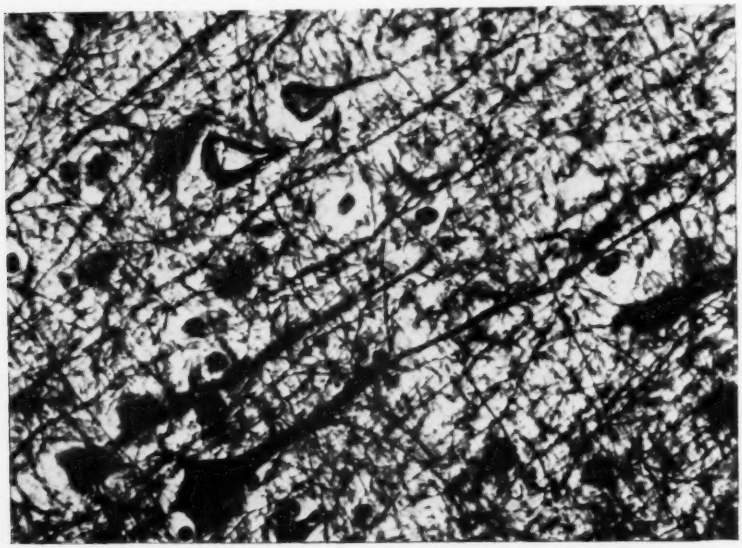


Fig. 2.—*Frontal Cortex :* showing neurofibrillary changes in the third layer. (Hortega's double impregnation ; high power.)

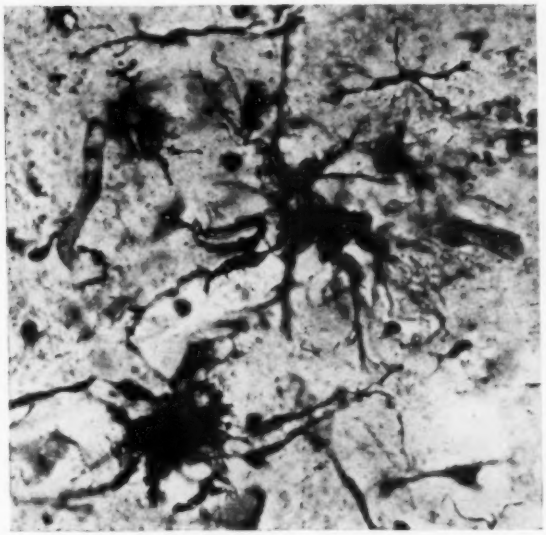


Fig. 3.—*Cornu Ammonis :* modified mesoglial elements are to be seen in the earliest stage of plaque formation. (Hortega's method for microglia ; high power.)

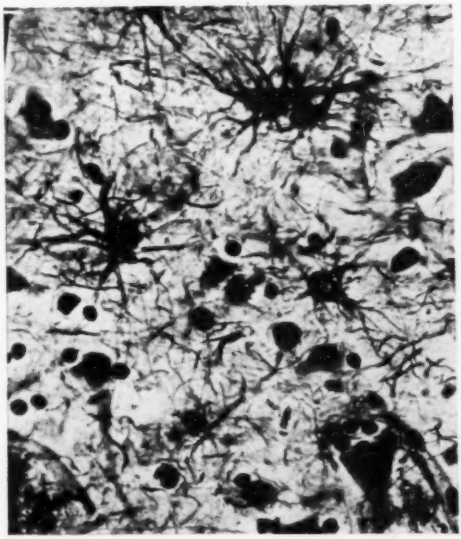


Fig. 4.—*Frontal Cortex :* reactive gliosis in an area of extreme neuronal degeneration. The astrocytes are of the fibrous type and one of them has just undergone fission. (Hortega's silver carbonate method for astroglia ; high power.)

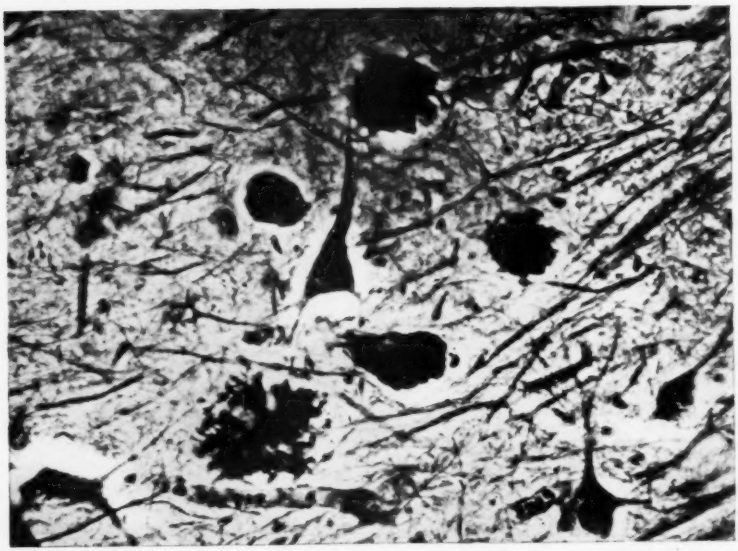


Fig. 5.—*Fascia Dentata :* three small senile plaques can be seen in close proximity to atrophying nerve cells. (Bielschowsky-da Fano silver impregnation ; high power.)

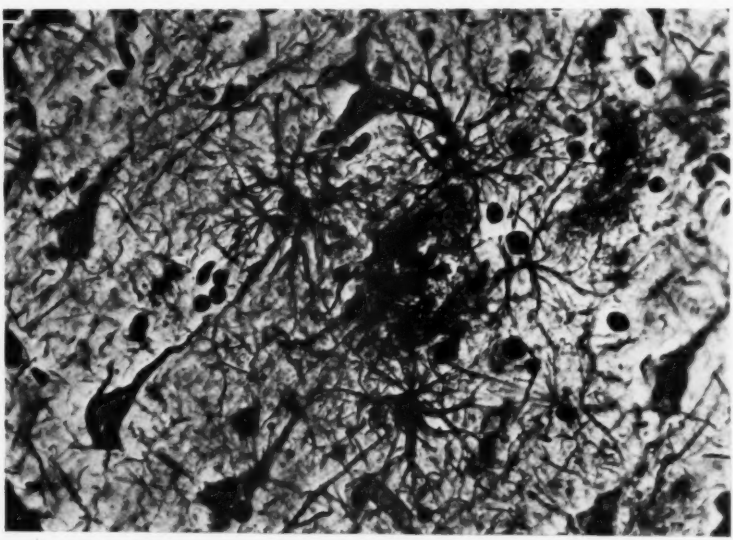


Fig. 6.—*Frontal Cortex :* showing condensation of fibrous astroglia around a plaque which shows in its centre modified mesoglial elements. Note neurofibrillary alterations. (Hortega's silver carbonate method for astroglia ; high power.)

layers being affected ; nerve cells are reduced in number and what remain are atrophied or show nuclear alterations and neurofibrillary changes in the form of well-marked " loops " and " tangles." Microglial elements, often extremely modified, can be seen in relation to the plaques and also to some of the atrophied nerve cells. The astroglia is increased in amount, particularly in the superficial and subcortical white matter, and is of the fibrous variety. The cerebral capillaries show only a little thickening and practically no pericapillary fibrosis. The leptomeninges over the frontal poles reveal chronic fibrous thickening. Plaques were not found in the basal ganglia, mid brain, pons, or medulla. The choroid plexus showed no abnormality other than the presence of some corpora amylacia.

Commentary

In the family described by Lowenberg and Waggoner, four out of five siblings and their father were affected, succumbing at the ages of 34, 37, 35, 36, and 33 respectively ; the fifth sibling had met with a violent death and there was no record of any mental abnormality. In each case the illness appears to have been more or less identical, although the duration varied from 2 to 6 years. The brain of the youngest of the four siblings, whose illness lasted 6 years, was studied carefully by these authors, and the findings were typically those of Alzheimer's disease with its extensive degeneration of cortical neurones and the presence of numerous plaques ; an authoritative description of the naked eye findings of the brain of the third sibling, which the authors read, suggests that the histology would have proved similar to that of their patient. It is interesting to note that the parents of the father were first cousins, as in the case of our patient.

The individual pathological features of Alzheimer's disease are known to occur in other disease processes, but the association of widespread neurofibrillary alterations and a superabundance of senile plaques is highly characteristic of this presenile dementia.

Nevertheless, Jervis and Soltz (1936) have maintained that an adequate morbid histology of this disease in the absence of a typical clinical picture is insufficient evidence for establishing the diagnosis. Without attempting to challenge these criteria of diagnosis and without venturing into a discussion on the subject of possible variations in the clinical picture, we consider that the clinical findings in our patient are compatible with the suggested diagnosis, and the widespread cortical changes are in keeping with the extreme intellectual impairment and destruction of personality which were the essential features of this case from the inception of the illness. With regard to the three male members of the previous generation, we are on less certain ground, as the histories available are inadequate. The fact remains, however, that each one of them presented symptoms of ingravescent disturbance of cortical function which would be consistent with the relentless progress of a widespread and slowly developing destruction of cortical neurones. If we disregard for the moment the case of the third sibling who, after the disease had progressed for

two years, met with a fatal accident possibly the direct result of his oncoming dementia, we still have two members of this generation who suffered from a progressive dementia which proved fatal in four years. It may be argued that the second of these is unlikely to be a presenile dementia because the age of onset was 63, and the presenium is generally regarded as ceasing at the age of 60. Some authors, however, allow the presenium to extend to the age of 65. We feel that there cannot be any arbitrary age limit between the presenium and senium, because the rate of ageing varies so considerably in different families and individuals. Also, there is more than a difference in age onset between Alzheimer's disease and senile dementia ; it is a question of degree. The dementia in the latter is seldom so profound as is usual in the former disease, a fact which is in keeping with the difference in the extent of degeneration of cortical neurones. Moreover, the symptomatology of senile dementia is seldom so widespread in its first years as in Alzheimer's disease and death is less often the result of the decorticating process than of some intercurrent illness. In the case of the second sibling, the disease so resembles that of the eldest brother that there can be no doubt that the underlying cause was the same. If the Alzheimer's symptomatology be regarded as a reaction by disturbance of personality and impairment of intellect to a pathological process in the brain tantamount to abnormal ageing and possibly due to intrinsic (e.g. abiotrophic) or extrinsic factors, then the later age of onset in this second member of the family would suggest a greater individual resistance to this familial weakness.

Summary

1. A case of Alzheimer's disease is described, the clinical and histological findings being typical.

2. Perusal of the family history reveals the fact that three out of four siblings of the previous generation, including the father of our patient, suffered from a presenile dementia, which in all probability, was identical with that of our patient.

3. As in the case of familial Alzheimer's disease, described by Lowenberg and Waggoner, the parents of the first affected generation were cousins.

We wish to express our thanks to Dr. F. R. King, Medical Superintendent of Peckham House, for permission to publish the case, to Dr. A. O'Neill, Medical Superintendent of Napsbury Hospital, and to Professor Hugh Cairns for the interest they have taken and for laboratory facilities granted for this study, also to Dr. P. del Rio Hortega for his unfailing kindness and help in the preparation of the histological sections and photomicrographs.

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ARHINENCEPHALY

BY

R. M. STEWART

(RECEIVED 27TH APRIL, 1939)

No human brain has yet been described in which all the structures which are believed to be subservient to the sense of smell have been absent, and consequently the designation " arhinencephaly " is misleading in that it suggests complete absence of a functional unit. In the majority of recorded cases the maldevelopment present has been either a partial or a complete absence of the olfactory bulbs and parts of the hippocampal formation with its association and commissural systems.

In this limited sense the term " arhinencephaly " may perhaps be sanctioned on the grounds that it affords a concise and convenient title for a condition which otherwise would be difficult to define within the compass of a few words.

Report of case

H.E.B., a male idiot aged 17 years, was admitted to Leavesden Hospital on 10th August, 1926. Height : 49 in., Weight : 4 st. 7 lb. He was completely helpless, dirty in habits, unable to speak, feed himself, or to walk without assistance. He sucked his fingers and salivated constantly. A right internal strabismus was present. Physically he was in poor condition, with cyanosed hands and feet. Major epileptic fits occurred about once a month. In May 1929 he developed physical signs of pulmonary tuberculosis. A month later a swelling appeared over the left parietal eminence ; on 8th November 1 ounce of thick pus was evacuated from it. A diagnosis of Pott's puffy tumour was made. Death from hæmoptysis occurred on 14th November.

Post Mortem.—An autopsy was held 19 hours after death. The body was that of an emaciated young adult male of small stature. Both lower limbs showed contractures at the knee-joints. A pear-shaped parietal tumour firmly attached to the scalp was found to contain semi-solid caseous material. At its base a circular area of caries of the parietal bone was present with slight downward projection of the inner table, to which the thickened dura mater was firmly adherent. Scrapings from the carious area revealed large numbers of tubercle bacilli.

The pia mater was diffusely thickened, but showed no adhesions or evidence of inflammation at the base. Both lungs were in a state of extensive tuberculous consolidation with cavity formation. The liver was the seat of amyloid degeneration. The other organs showed no changes of importance.

Description of brain

Macroscopic Examination.—The brain is exceptionally large and heavy, its weight, including pia-arachnoid, being 1,506 gm. Right cerebral hemisphere,

645 gm. ; left cerebral hemisphere, 649·5 gm. Cerebellum and brain stem, 211·5 gm. The convolutions are large, of simple pattern, and fairly symmetrical. On the right hemisphere the pre- and post-central gyri pursue a normal course ; on the left side their conformation is most irregular.

All the cranial nerves, with the exception of the olfactory, are unusually well developed ; the fossa interpeduncularis is very deep, the orbital surfaces

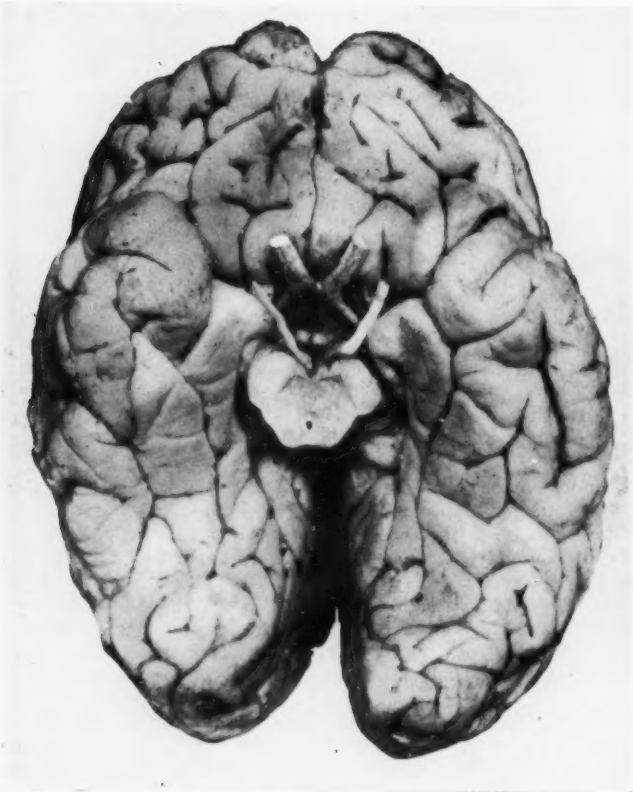

Fig. 1.—Base of brain, showing complete absence of olfactory bulbs and tracts. Note the presence on the orbital surfaces of the frontal lobes of short irregular sulci ; there are no true gyri recti.

of the frontal lobes are large, and there is complete absence of the bulbus and tractus olfactorius on both sides (Fig. 1). The sulci present on this surface are short and irregular in form ; on the right side a sulcus runs forwards and outwards for about 2 cm. and terminates by dividing into two short and obliquely placed branches : on the left side a shorter sulcus ends by dividing into two small branches more transversely placed than on the opposite side. It is doubtful whether the short and broad gyri bounded by these sulci can be

looked on as gyri recti. There is no olfactory trigone, no area parolfactoria, no anterior perforated substance, and no diagonal band of Broca.

On the mesial surface of each hemisphere the most striking feature is the diminutive size of the divided corpus callosum, which has a length of only 6 cm. (Fig. 2). Although underdeveloped as a whole, it is particularly its posterior half which is thin and attenuated, the splenium being no thicker than the middle third of the body ; ending immediately above the pineal body, it completely fails to cover the pulvinar ; the latter forms a conspicuous prominence on the mesial aspect of the hemisphere. The smallness of the corpus callosum gives the impression of an unusual expanse of parietal and occipital cortex behind it. On this aspect the gyrus cinguli is seen as a well-developed

Fig. 2.—Mesial aspect of cerebral hemisphere. The corpus callosum is rudimentary and the absence of the splenium leaves the pulvinar, pul., exposed ; on the infero-mesial aspect a well-developed hippocampal gyrus, h., and uncus, u., are conspicuous. Other structures depicted are the gyrus subcallosus, g.s., the anterior pillar of the fornix, f., the anterior commissure, a., the corpus mammillare, c.m.

convolution, but unusually free from secondary sulci. The gyrus hippocampi is likewise conspicuous and possesses a well-marked uncus, bent sharply in the usual manner. There is, however, no band of Giacomini and the gyrus intralimbicus, gyrus semilunarus, and gyrus ambiens cannot be defined.

The fimbria, the body of the forni, its anterior pillars, and the septum pellucidum are readily recognized, and are of normal appearance. The gyrus dentatus is likewise present, but it conveys the impression of underdevelopment, being decidedly less prominent than in the normal brain. Other areas connected with the olfactory system which cannot be identified are the gyrus fasciolaris and the gyri Andreæ Retzii. While the massa intermedia is of normal dimensions, the anterior commissure is perhaps thinner than normal, though

in a vertical coronal section through the hemispheres in this plane there is no difficulty in following its temporal fibres as they pass outwards horizontally beneath the lenticular nucleus. In the same coronal section it is possible to identify the nucleus amygdalæ.

Careful scrutiny of the dorsal surface of the corpus callosum fails to reveal any evidence of the indusium griseum and striæ medullares longitudinales.

Other tracts forming part of the olfactory projection system which can be recognized are the tænia thalami and the tænia semicircularis, the latter accompanied by the striate vein.

TABLE SHOWING THE DEFECTS PRESENT IN THE RHINENCEPHALON.

Olfactory bulbs	Absent.	Gyrus ambiens	Not identified.
Olfactory tracts	Absent.	Gyrus dentatus	Reduced in size.
Olfactory trigone	Absent.	Band of Giacomini	Absent.
Area parolfactoria	Absent.	Gyrus supracallosus	Attenuated.
Anterior perforated substance	Absent.	Gyrus fasciolaris	Absent.
Gyrus subcallosus	Normal.	*Gyri Andreæ Retzii	Absent.
Diagonal band of Broca	Absent.	Fimbria	Normal.
Gyrus cinguli	Normal.	Body of fornix	Normal.
Isthmus hippocampi	Normal.	Anterior pillars of fornix	Normal.
Gyrus hippocampi	Normal.	Septum pellucidum	Normal.
Gyrus uncinatus	Normal.	Anterior commissure :	
Gyrus intralimbicus	Not identified.	1. Olfactory fibres	? Absent.
Gyrus semilunaris	Not identified.	2. Temporal fibres	Normal.

Microscopic Examination.—An examination of Nissl preparations made from the superior frontal gyrus, the pre- and post-central gyri shows changes which are characteristic of profound idiocy. Many of the pyramidal nerve cells show poorly developed cell bodies with irregular alignment and an actual numerical deficiency, especially in layers 3 and 4. Various stages of chronic chromatolysis can be found. The cortical vessels show no change, but there is a considerable degree of marginal gliosis.

Corpus callosum : coronal sections of the body of the corpus callosum stained by the method of Loyez show a thin stratum of fibres running in a longitudinal direction immediately above the dense layer of transverse commissural fibres. This stratum, though not uniform in thickness, shows no aggregation into strands. In other words, the medial and lateral longitudinal striæ are represented only by a thin layer of fibres. Normally, the nervi Lancisii are accompanied by small oval ganglion cells which constitute the indusem griseum, but none of these can be found.

Frontal section through the area dentata and gyrus hippocampus immediately caudad to the uncus (Fig. 3). The Hippocampal gyrus. Its cortex is well developed both in the subiculum and præsubiculum : its thickness, 2·3 mm., is within the limits of the normal and its peculiar cellular lamination is well defined. Thus from without inwards, it is possible to recognize : (1) a broad plexiform layer ; (2) nests or islets of large and small stellate cells constituting the so-called glomeruli ; (3) a thick layer of regular and slender

* Frequently absent in normal brains.

pyramidal cells ; (4) a thin compact layer of densely arranged large pyramidal cells ; (5) a broad layer of spindle-shaped cells. The tangential fibres in the plexiform layer of the subiculum and præsubiculum stain uniformly with myelin sheath stains and are not noticeably fewer than normal.

Fig. 3.—Microphotograph of the hippocampal gyrus, h.g., and the dentate gyrus (fascia dentata) f.d. Both areas show a normal cellular lammellation, but there is a general reduction in the size of the dentate gyrus. p. : pyramidal cells of fascia dentata. g. : stratum granulosum. a. : alveus. Cresyl violet stain : X7.

Fascia Dentata : even without comparison with the normal control it is obvious that the dentate gyrus is considerably reduced in volume, and this reduction affects all its strata except perhaps the layer of granular cells (stratum granulosum) in which the normal arrangement of densely packed small cells appears to be preserved (Fig. 4). Encircled by the stratum granulosum, the medium sized pyramids, distributed in the normal irregular radiating manner, show no numerical deficiency, though owing to the small volume of the entire fascia dentata their total number must be much less than in the normal brain. The layer of large pyramidal cells lying internal to the medullary centre of the hippocampal gyrus is, however, markedly narrowed, though no cell gaps can be seen ; the stratum radiatum formed by their processes is poorly defined. The third and fourth layers, stratum granulosum and stratum laciniosum respectively, are likewise difficult to distinguish. The superficial layers of

nerve fibres are slightly thinner than normal. The nerve fibres which constitute the alveus stain rather poorly by Loyez' method and appear finer in comparison with those in normal sections.

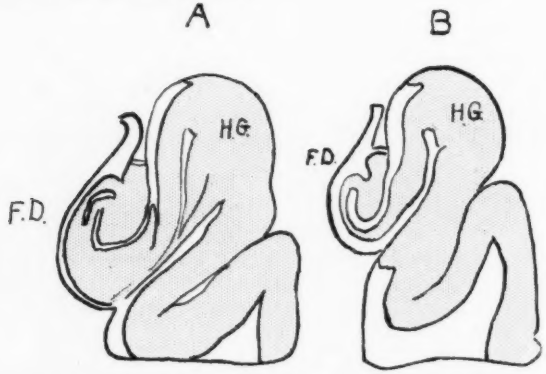

Fig. 4.—Outline drawings of unstained blocks of the hippocampal and dentate gyri : (*a*) from normal control ; (*b*) from arhinencephalic brain. The dentate gyrus is considerably better, developed in the control block (a). h.g. : hippocampal gyrus. f.d. : dentate gyrus. X2½.

There is no noticeable change in the fimbria.

Glia : There is no evidence of fibrillary gliosis in either the hippocampal convolutions or the fascia dentata.

Discussion

Following Schwalbe and Josephy (1913), arhinencephalic brains may conveniently be divided into two groups :

1. Cyclopian brains, complete or partial, in which an arrest of growth has taken place at the cephalic end of the embryonic plate, with fusion of the olfactory bulbs and optic vesicles.
2. Brains characterized by absence of the olfactory bulbs and tracts without gross malformation of the cerebral hemispheres.

Cyclopia : Kundrat (1882) has dealt exhaustively with this type in his monograph " Arhinencephaly," and subsequent contributions have been made by Schwalbe and Josephy, Ranke (1913), Klopstick (1921), Van Duyse (1921), Rothschild (1924, 1927), Gamper (1926), Politzer (1930), and Henze (1934).

The salient features of the cyclopian brain include incomplete division of the end brain, hydrocephalus, defects of the eyes and optic tracts, and absence of the olfactory tracts.

Closely related to the typical cyclopian brains are those in which, although there is no fused or median eye, the end brain remains incompletely divided. To this category belong the arhinencephalic brains described by Goldstein and Riese (1925), Kummer (1923), de Jong (1927) and Kuhlenback and Globus (1936).

Absence of the olfactory bulbs and tracts without gross malformation of the cerebral hemispheres : arhincephalic brains of this type are unquestionably rarer than those in the former group, and probably not more than fifteen examples have been placed on record. Many of the accounts are fragmentary and in only a few have adequate histological investigations been carried out. The latter are referred to below.

In most of the lower vertebrates smell is the dominant sense, and in consequence the entire cerebral hemisphere is concerned with the perception of smell ; in other words, in macrosmatic vertebrates the hemisphere is primarily an olfactory receptive nucleus. On the other hand, in the most highly organized types of brain—those of man and the other primates—to whom the sense of smell is relatively unimportant, the portion of the brain believed to be concerned with olfaction is relegated to a comparatively small area. None the less, even in the human brain the rhinencephalon is by no means inconspicuous. The limbic lobe which constitutes the central or cortical part of the rhinencephalon occupies an area of considerable extent on the mesial aspect and from the point of view of size the hippocampal gyrus—one of its constituent parts—is quite as impressive as, say, the motor cortex in the neopallium. But whether in man olfactory impressions are the only ones to be discharged into the whole limbic lobe is very debatable. Indeed, taste and smell are so closely interrelated in the processes of nutrition that it may well be that research will one day show that this part of the rhinencephalon is concerned just as much with gustatory as with olfactory reactions. A survey of the anatomical findings in the literature devoted to arhinencephaly indicates that they afford little uniformity on which to base a confident pronouncement on the cortical representation of smell. It is perhaps hardly necessary to state that conclusions drawn from naked-eye inspection of the brain unsupported by histological study at the most possess a limited value ; unfortunately the majority of the recorded cases of arhinencephaly fall into this category. Prominent among the notable exceptions is the remarkable case described by de Jong (1927), in which although no trace of the olfactory bulbs and tracts could be found, not only were the cornu ammonis and fascia dentata present but on histological investigation these areas were found to be actually better developed than in a normal brain of the same post-natal age.

On the other hand, a definite reduction in the size of the cornu ammonis has been reported on more than one occasion. In the brain described by Tanaka (1920) there was evidence of sclerosis in the cornu ammonis, accompanied by atrophy of the hippocampal gyrus on both sides. Tanaka's patient was, however, an epileptic and since sclerosis in this territory is not infrequently determined by the functional disturbance of the circulation which accompanies convulsions, it is quite possible that the changes in his case were related, not to a primary arrest of development of the olfactory bulbs, but to the long-standing epilepsy.

In the first of Uyematsu's (1921) two cases of unilateral absence of the olfactory bulb some degree of sclerosis of the homolateral cornu ammonis was also present, the corresponding convolution on the other side being normal.

But in this case, too, there was a history of convulsions ; and as in cases of even long-standing epilepsy sclerosis of Ammon's horn may remain strictly unilateral, it cannot be claimed with any degree of certainty that absence of the olfactory bulb conditioned the sclerosis. As in Tanaka's case, this may have been epileptic in origin.

In his second case there was also a history of seizures. Histological examination revealed slight degeneration of the cornu ammonis, equal in intensity on the two sides. The author concludes that greater importance is to be attached in both cases to the more advanced regressive changes in the pyriform lobe, which he regards as an end result of the loss of the peripheral olfactory apparatus.

In the brain of the epileptic idiot reported in this communication there was also a slight reduction in the size of the cornu ammonis on both sides, but without any evidence of neuroglial sclerosis, the changes being, in fact, entirely quantitative ; consequently they may legitimately be held to be related to the absence of the olfactory bulbs and tracts.

An extremely interesting feature in this case was the persistence of a number of foramina in the cribriform plate of the ethmoid notwithstanding complete absence of the olfactory bulbs. Such a finding, which was also present in the cases described by C. Bernard (1856), Duval (1884), and Mirsalis (1929), clearly indicates that at one stage of development olfactory nerves must have been present. Their development in the sixth week of fœtal life precedes the formation of the cerebral membranes and cribriform plates (Keith, 1933), and consequently the foramina may owe their formation to the penetration of nerve fibres. From embryological studies it is apparent that the development of this part of the brain is peculiar in that the olfactory sense epithelium and olfactory nerves develop separately from the central part of the rhinencephalon.

In the development of the forebrain Ariens Kappers (1929) attributes a preponderant role to the paired olfactory placodes. When the placodes fail to exert that influence arhinencephaly is established and pairing of the cerebral vesicles does not take place. As proof of this, he cites the experiments of Burr (1924) on amphibia. On transplantation of one olfactory placode to another part of the head he was able to observe the hemispherical wall growing out to the transplanted placode. But as Kuhlenbeck and Globus (1936) point out, though Kapper's theory affords an explanation for the lack of development of the olfactory bulbs and tracts, it does not afford a satisfactory explanation of why arhinencephaly should sometimes be associated with normally developed hemispheres and sometimes with a highly defective end brain.

From an analysis of the observations cited in this paper, it is clear that complete absence of the olfactory bulbs and tracts, which must of necessity deprive the pallial rhinencephalon of olfactory impulses, in no way excludes the possibility of normal development of certain of its complex divisions. Thus, among the possibilities, are : (*a*) no naked eye abnormality, as in Issajew's (1932) case ; (*b*) an actual overdevelopment of cortical olfactory areas, such as de Jong has described ; (*c*) degenerative changes in the hippocampal

convolution, with or without sclerosis of the cornu ammonis, as in the reports by Tanaka and Uyematsu ; (*d*) changes almost entirely confined to the dentate gyrus, as in the cases described by Oldberg (1934) and the writer.

Such findings permit the conclusion, previously arrived at by Ranke (1913) and quoted by Kuhlenbeck and Globus, that in arhinencephaly cortical differentiation is to a high degree independent of the differentiation of corresponding peripheral centres. With this consideration in mind, it follows that our knowledge of the functional significance of the rhinencephalon is not likely to be advanced by the study of developmental defects in the human brain. On the other hand, if it be permissible to accept the homologies of comparative neurology, considerable importance must be attached to defects in the fascia dentata, for in anosmatic animals, such as the dolphin, this structure is the only central part of the rhinencephalon which is wholly wanting (Hill, 1893). But, as Herrick (1933) remarks, even in those animals in which the rhinencephalon is highly developed, olfactory sensation in never an efficient localizing sense. Odours may be discriminated, but they cannot be accurately localized without the use of other senses, and accordingly none of the olfactory areas can be said to be truly olfactory centres in a sense comparable to centres for vision or hearing ; their function is associative rather than initiative or interpretative. If this be true of macrosmatic mammals it must obviously apply with even greater force to man, who is emancipated from the dominating influence of olfactory impressions.

Summary

The brain of an epileptic idiot is described in which there was complete absence of the olfactory bulbs and tracts. No abnormality could be found in the hippocampal convolutions but on both sides the fascia dentata was considerably reduced in size. Histological examination confirmed these observations.

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THE FUNCTIONAL RESPONSES OF THE SYMPATHETIC NERVOUS SYSTEM OF MAN FOLLOWING HEMI-DECORTICATION *

BY

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(RECEIVED 3RD MAY, 1939)

THE relation of the cerebral cortex to the activity of the sympathetic nervous system is not yet fully clear. The clinical and experimental observations, which have recently been reviewed by Kennard (1937), have been conflicting, and there have been few quantitative determinations of the effects of cortical stimulation and ablation upon the functions of the human sympathetic nervous system.

Many indices of sympathetic function have been used in the past, peripheral vascular changes, the psychogalvanic response, sweating, pupillary changes, and visceral contraction being the most usual. The " galvanic skin reflex " is dependent on an intact sympathetic nervous system, and may be accurately measured. It has therefore been widely used as an index of sympathetic activity in studies of cortical function. In 1905 Bechterew stimulated the medial part of the anterior sigmoid gyrus in the cat and caused sweating of the pads. The response was greater on the contralateral side. Winkler (1908) obtained a symmetrically equal response to similar stimulation. In 1930 Langworthy and Richter found that faradic stimulation of cortical areas similar to those used by Bechterew lowered the skin resistance of a cat's pads. The response was bilateral, but was greater on the contralateral side. Schwartz (1937) continued the investigation by excising known areas of the cortex in cats, and observed the " psychogalvanic response " to various stimuli for three to six months afterwards. After unilateral removal of the area frontalis agranularis, peripheral pain and stimuli associated with fright caused no response on the contralateral side, but responses to sudden pressure on the limb remained symmetrically equal. Excision of cortex elsewhere did not modify the response in any way, so that Schwartz postulated two types of response—a " segmental galvanic reflex " independent of cortical control and a " psychogalvanic reflex " with a true cell station in the area frontalis agranularis.

* Work undertaken while Dr. Williams held a Rockefeller Travelling Fellowship in Neurology and Mr. Scott a University of Toronto Fellowship in Physiology.

This implied a discrete cortical centre with sensory afferents and sympathetic efferents.

Stürup *et al.* (1935) investigated the effect of diverse cerebral lesions on the vasomotor response to peripheral stimulation in man. They concluded that the efferent pathway used by the response had not been involved in any of the lesions. They were therefore unable to advance any evidence in favour of cortical representation of the response. Marquis and Williams (1938) found that in man lesions of the sensory pathway below the thalamus modified the vasoconstrictor responses to peripheral sensory stimulation. The changes produced were related to the observed changes in sensation. Lesions of the thalamus, internal capsule, and cerebral cortex did not cause such alterations in the vasoconstrictor response. They therefore concluded that the reflex arc mediating the vasoconstrictor response to pain did not ascend above the hypothalamus, but they pointed out that the few cases of cerebral damage reported were not adequate, and did not exclude all areas of the cortex from participation in the vasomotor responses. Their observations suggested that the afferent pathway was the spino-thalamic tract and that its highest cell station was situated below the thalamus.

These observations show that there is an apparent difference between the results of similar experiments in animals and in man. The recent observations of Pinkston and Rioch (1938) on skin temperature following cortical ablation in monkeys contrast so strikingly with their earlier observations on dogs (Pinkston, Bard, and Rioch, 1934) that the authors postulate a species difference. As such wide differences as they have found can occur, it is obviously undesirable to apply to man information derived from animal experiments in this field. In order to determine if there is a cortical sympathetic centre in man, more extensive and exact cortical ablation would be required. Although the psychogalvanic and vasomotor responses to peripheral stimulation have so many common features, it is possible that they may use different pathways in the central nervous system. It would therefore be desirable to investigate them simultaneously in the same subject.

A girl who had had a complete hemidecortication two years previously was made available for study. Sympathetic activity, expressed as peripheral vasomotor responses and "galvanic skin reflexes" in response to various stimuli, were therefore investigated. It is the purpose of this paper to present the results obtained and to correlate them with previous observations. A report of the case used in these experiments has been presented by McKenzie (1938) and will be published in detail later. Only sufficient clinical data necessary to establish the state of the subject at the time of the experiment will therefore be presented. The subject, a girl of 20, had a severe head injury when 3 weeks old, followed 6 hours later by fits which appear to have been focal, beginning in the left face. She was subsequently found to have a left hemiplegia, which persisted throughout life. The fits continued, but changed in character, and when 5 years old she was having several *grand mal* seizures and "psychic variants" daily. There was no apparent mental deterioration. When 16 years old she came to the Toronto General Hospital and was found to have a left

hemiplegia, with a typical gait and posture. The paralysed extremities were smaller than those on the right and the skin of the hand was soft and smooth. There was fairly good movement of the large joints. She walked moderately well, but there was no voluntary movement of the hand or foot. There was absolute loss of cortical types of sensation in the left hand and foot, and a left homonomous hemianopia. Encephalography showed an extensive cerebral

Fig. 1.—The lateral aspect of the excised hemisphere. Measurements are in cm.

defect over the area of distribution of the right middle cerebral artery. On 22nd June, 1938, a complete right cerebral amputation through the internal capsule was performed by Dr. K. G. McKenzie. The operation report reads : " The whole of the right cerebral hemisphere was removed, with the exception of a very small amount of cortex representing the under surface of the frontal lobe adjacent to the anterior part of the sella, and a thin rim of temporal lobe adjacent to the optic thalamus." The extent of the hemidecortication is well seen in Figs. 1 and 2.

Following operation there was no change in the hemiplegic state, but the fits ceased completely. With the cessation of the fits, however, the girl's health improved, and when investigated her physical well-being and mental alertness were striking. She co-operated intelligently and understood the purpose of the investigations. There was a spastic left hemiplegia with characteristic posture and gait. Voluntary movement of the left hand and foot was impossible, but at the large joints movement was fairly good. Dr. E. H. Botterell, in an investigation to be published in detail later, found that the sensation to painful and thermal stimuli was normal throughout, while there was absolute loss of appreciation of light touch, joint movement, spatial

perception, and tactile discrimination in the affected hand and foot. All forms of sensation were normal on the opposite side of the body.

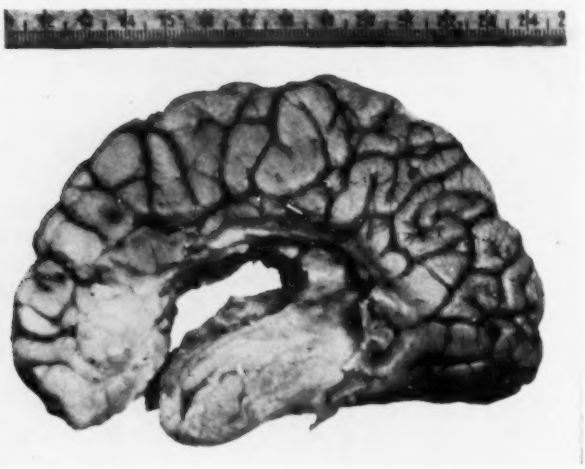

Fig. 2.—The mesial aspect of the excised hemisphere.

Method

The experimental procedure was identical with that which has been described before (Marquis and Williams, 1938). The patient, to whom the method had previously been described, sat comfortably at rest with the hands supported level with the heart, and with the eyes closed. The room was darkened and made as quiet as possible. Stimuli were applied under the same experimental conditions each day, and several rest periods were allowed to reduce fatigue of the patient to the stimuli. Various stimuli were used. A known intensity of pin-prick, applied with a modified Head algesiometer which has been described (Marquis and Williams, 1938), and melting ice in a flat-bottomed copper calorimeter were used as cutaneous stimuli. Sudden noise, apprehension, mental exertion, and deep inspiration were also used. These stimuli were applied in a predetermined random order to obviate anticipation. The cutaneous stimuli were applied with equal frequency to both sides.

Vasomotor Responses.—Small glass plethysmographs sealed with vaseline on both middle fingers were connected independently by pressure tubing through a closed-air system to sensitive tambours. Mirrors on the tambours reflected a beam of light on to moving bromide paper. Respiratory phases, time in seconds, and signals were also recorded. Vasodilatation, to ensure a constant background for the vasoconstrictor response to be measured, was obtained by immersing the legs in water at 40°–45° C. Time was allowed between stimuli for return to the basal dilated state.

Psychogalvanic Responses.—These responses were not obtained at the same time as the vasomotor responses, as they are greatly modified by the sweating which accompanies the rise in body temperature. Except that the subject sat at room temperature without immersion of limbs, the experimental conditions were identical. The recording apparatus consisted of an Einthoven string galvanometer (Cambridge Model). The shadow of the string was recorded on moving photographic paper. The electrodes used were small squares of zinc plate (3 × 3 cm.) to which leads had

been soldered. These were applied to the dorsal and palmar surfaces of each hand after being moistened with zinc sulphate jelly. They were held in place by gauze pads and loose elastic bands. Care was taken not to obstruct the circulation or to cause discomfort. By means of a triple position selector switch the string could be quickly connected to either hand or to the control board for calibration. The tension of the string was adjusted till a potential of 1 millivolt caused a deflection of 10 millimetres on the photographic paper. Seconds and signals were recorded.

Results

Vasomotor Responses.—The subject at the commencement had the peripheral vessels in a constricted state, but on immersion of the feet in hot water, dilatation of the vessels and sweating took place on both sides of the body in a normal manner. It was not found possible to compare the vasodilator responses from the fingers of each hand to the rise in blood temperature, as the volume of the middle finger on the hemiplegic side was about 70 per cent. that of the normal. Thus a correspondingly smaller plethysmograph had to be used. With plethysmographs of equal volume, the average response to deep inspiration from the hemiplegic side was just 70 per cent. that of the normal, but with a smaller plethysmograph on the atrophic finger the recorded bilateral responses were similar in character and were approximately equal (Fig. 3). As the afferent

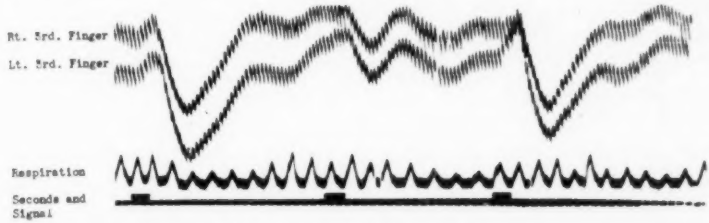

Fig. 3.—A record is shown of the volume of both middle fingers, decrease being downwards, with phases of respiration, time in seconds, and signals. The record reads from left to right. At the first signal the abnormal forearm was pricked, at the second signal ice was applied to the normal knee, and at the third signal the normal forearm was pricked.

pathway for the response to deep inspiration must be bilateral, it is probable that this disparity resulted from lack of vascular bed in the small immobile finger. The results obtained from stimulation of the skin with a known intensity of pin-prick and of cold are presented in the table on p. 318.

In this table the statistical significance of the difference between means was determined by Fisher's (1932) method for small samples. σ denotes the standard deviation of the individual samples from the mean, t the ratio of the difference to the estimated standard error of that difference, and P the probability of the observed difference arising by chance. When P is greater than 0·02, which indicates that the given difference might be expected to arise by chance less than twice in 100 random samples, the difference is not significant. It will be readily seen that none of the recorded differences are large enough to be outside the limits of chance. As has been shown (Marquis and Williams, 1938) 10 to 20 similar adequate stimuli were necessary in this procedure to furnish statistically significant results. A sufficient number of responses to pin-prick

TABLE 1.—THE VASOCONSTRICTOR RESPONSES TO MEASURED STIMULI OF PAIN AND COLD APPLIED TO THE NORMAL AND AFFECTED SIDE OF THE HEMIDECORTICATE SUBJECT

EXPERIMENT	STIMULUS	STIMULATION OF NORMAL SIDE			STIMULATION OF ABNORMAL SIDE			DIFFERENCE (mm.)	t	P
		NUMBER	AVERAGE RESPONSE (mm.)	σ	NUMBER	AVERAGE RESPONSE (mm.)	σ			
1	Pin-prick	28	8·0	8·86	18	10·0	5·75	+2·0	0·93	0·7
2	Pin-prick	32	16·4	11·4	42	12·8	10·9	−3·6	1·23	0·2
1 and 2	Pin-prick	60	12·4	—	60	11·9	—	−0·5	—	—
1 and 2	Cold	14	16·8	10·2	14	19·3	11·6	+2·5	0·60	0·5

In this and the following tables the deflection is measured in millimeters; sigma (σ) is the standard deviation from the mean, t the ratio of the observed difference to the standard error of that difference, and P the probability of the observed difference arising by chance (see text)

were obtained to present each day's data separately. Neither day's results show a significant inequality. Grouping the two experiments reduces the experimental error and shows a high degree of equality. Similarly, responses to cold which were grouped to make the number adequate show no significant difference between the responses from both sides. The responses to noise, fright, and mental exertion did not show any obvious disparity, although their number was not large enough to be quantitated.

Psychogalvanic Responses.—Preliminary investigations of a normal subject showed that even under the stable experimental conditions employed the response was very variable, so that an average of several stimuli was needed to obtain accurate comparison of the responses from both sides of the body. In measuring the size of the response, the total amount of deflection of the image of the galvanometer string was determined, and the various groups of results averaged and subjected to the same statistical analysis as were the vasomotor responses (Fig. 4). The effects of stimulation of each side of the body, and the responses from each hand were averaged independently.

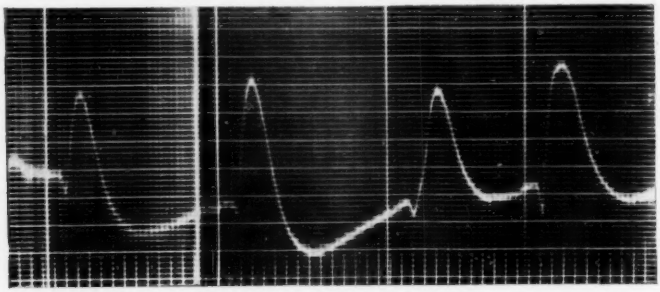

Fig. 4.—A record of the potential changes of the palm of the left hand in response to pin-prick of the right side of the neck, of the left knee and of the right knee, and lastly in response to a sudden noise. The record reads from left to right. Time is in seconds. Approximate time of stimulation is shown by a vertical line. 1 cm. deflection is equivalent to 0·1 millivolt, the narrow horizontal lines being 0·1 cm. apart.

The results obtained from the normal control subject are contained in Table 2 and those from the hemidecorticate subject in Table 3.

TABLE 2.—COMPARISON AND STATISTICAL SURVEY OF GALVANIC SKIN RESPONSES TO STIMULATION WITH MEASURED PIN-PRICK ON BOTH SIDES OF THE BODY, AND OF THE RESPONSES OBTAINED FROM BOTH HANDS IN A NORMAL SUBJECT

PIN-PRICK ON RIGHT			PIN-PRICK ON LEFT			DIFFERENCE (mm.)	*t*	P
NUMBER	AVERAGE DEFLECTION (mm.)	σ	NUMBER	AVERAGE DEFLECTION (mm.)	σ			
12	7·1	6·47	12	6·0	5·68	−1·1	0·442	0·6
RESPONSE FROM RIGHT			RESPONSE FROM LEFT					
10	6·4	5·0	16	7·3	5·68	+0·9	0·45	0·6

TABLE 3.—RESULTS SIMILAR TO THOSE EXPRESSED IN TABLE 2, FROM THE HEMIDECORTICATE SUBJECT

PIN-PRICK ON NORMAL SIDE			PIN-PRICK ON ABNORMAL SIDE			DIFFERENCE (mm.)	*t*	P
NUMBER	AVERAGE DEFLECTION (mm.)	σ	NUMBER	AVERAGE DEFLECTION (mm.)	σ			
50	17·8	10·5	54	16·3	9·7	−1·5	0·789	0·4
RESPONSE FROM NORMAL SIDE			RESPONSE FROM ABNORMAL SIDE					
41	16·0	8·8	71	17·5	10·4	+1·5	0·81	0·4

It will readily be seen that in the normal subject the responses from stimulation on both sides of the body and the responses obtained from each palm do not show any significant difference. In the hemidecorticate subject there was a similar equality between the two sides of the body. The responses resulting from fright, apprehension, mental exertion, and deep inspiration, although too few to be averaged, did not show any apparent asymmetry, nor was there any asymmetry in their character or time relations.

Discussion

Marquis and Williams (1938) found that in five subjects with cerebral lesions causing sensory changes, the vasoconstrictor responses to sensory stimulation

were unaffected by the lesions. The sparing of the vasoconstrictor responses in these cases was most readily explained by the central arc for the vasoconstrictor response being complete below the thalamus. The possibility of a divergence of afferent sensory and afferent vasomotor fibres going to a specific centre could not, however, be excluded.

In this present case cortical removal had been as extensive and exact as in animal experiments, the only remnants of cortex left being adjacent to the anterior part of the sella and the lower part of the thalamus. It was therefore extremely unlikely that any ascending cortical afferent fibres had been spared It is possible that the vasomotor afferent fibres were using an hypothetical cortical " centre " in the ipsilateral hemisphere, as there was clinical evidence of widespread cortical damage since infancy. The chronicity was evident from the extreme gliosis seen in the removed hemisphere. Its total weight was only 126 gm., suggesting long-standing and diffuse atrophy. Botterell (1938) has shown that in this subject pain and thermal sensations were normal throughout, while true cortical sensations—the appreciation of light touch, small joint movements, spatial perception, and tactile discrimination—were completely absent in the hand and foot of the hemiplegic side. There was marked diminution of tactile discrimination on the hemiplegic side of the trunk and in the affected limbs. There had thus been little recovery of the true cortical types of sensation and consequently little evidence that the sensory afferents had any representation in the ipsilateral hemisphere. Even were there a degree of recovery of the cortical afferent system, this would be reflected in some inequality of the vasomotor responses, if they utilized cerebral pathways. The absolute equality of the vascular responses and the absence of recovery of cortical sensation make such a compensating mechanism unlikely, but suggests that the reflex arc under discussion cannot have had cortical afferents.

No accurate measurements of vasomotor activity in man following hemidecortication have previously been made, but Zollinger (1935) did not notice any apparent difference in the skin temperature of a patient who had survived hemidecortication for only a few days.

The " galvanic skin reflex " has been used in this investigation solely as a measurable result of activity of the sympathetic nervous system. The afferents for the response to peripheral stimulation are the somatic afferents. As with the vasomotor response a disparity in the results of stimulation on the abnormal side compared with the normal would indicate involvement of the afferent pathway for the response, while an inequality of the responses from each side of the body would indicate interference with the efferent pathway or effector mechanisms. The equality of the responses obtained from stimulation of each side of the body can only be explained by completion of the afferent pathway at a level lower than the cerebrum or by bilateral representation of the response in the cerebral cortex. Schwartz's observations on the cat, referred to above, point to specific unilateral localization in the cortex of the cell stations involved, but this disparity may be due to a species difference. However, none of the evidence which has been advanced to support a discrete cortical sympathetic cell station in man has pointed to a bilateral representation of that centre. The

alternative hypothesis, of generalized cortical projection to the sympathetic nervous system, would allow of hemidecortication without changes in the galvanic skin response of the contralateral side. This would explain the equality of the responses to bilaterally equal stimuli in the present case.

The same argument could be used for the efferent pathways. It has been pointed out that the skin of the affected hand was glossy and that the hand was atrophic. If this were to diminish the size of the responses, equality might be produced by overaction on the hemiplegic side, as suggested by Darrow (1932), who observed that the response was increased on the affected side in patients with cortical lesions who had no atrophy of the hemiplegic side. It is unlikely that the balance would be such as to cause the striking equality seen in Table 2, and furthermore the pattern of the responses and their time factors were also similar in the two hands. Thus the most plausible explanation of the bilateral equality of the afferent impulses and of the efferent responses would be that the pathway subserving the response did not reach the cerebrum.

It is evident that the cerebral cortex modifies sympathetic activity, for Doupe, Miller, and Keller (1939) found that the vasoconstrictor response to peripheral painful stimuli was diminished from areas which had been rendered hypalgesic by hypnotic suggestion. This diminution was only evident when the pain was sufficient to produce expressive signs of discomfort on stimulation of normal areas. They therefore thought that the emotional response to pain enhanced the vegetative response. As the appreciation of pain was unaffected in the present instance these observations do not contravert the conception of general cortical dominance over lower centres. On the other hand, no evidence can be obtained through the medium of the vasoconstrictor or galvanic skin responses of a localized cortical representation of the sympathetic nervous system, such as exists for sensation, voluntary movement, and the special senses in man.

Summary

The peripheral vasomotor reactions and the " psychogalvanic " responses have been investigated in a girl who had had a complete hemidecortication two years previously.

The equality of the responses from both sides of the body and from cutaneous stimulation of each side suggests that the reflex arcs used in these responses have no cortical cell station in man.

The investigation was performed in the Department of Physiology of the University of Toronto through the courtesy of Professor C. H. Best. We are indebted to Dr. K. G. McKenzie, who performed the hemidecortication, and who made the case and case records available for study ; Dr. E. H. Botterell, who carried out extensive sensory examinations ; Dr. D. Y. Solandt, in whose laboratory the work was undertaken ; and to Dr. W. F. G. Richardson for her technical assistance.

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SWAYBACK:

A DEMYELINATING DISEASE OF LAMBS WITH AFFINITIES TO SCHILDER'S ENCEPHALITIS AND ITS PREVENTION BY COPPER

BY

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From the Institute of Animal Pathology, Cambridge University

(RECEIVED 4TH AUGUST, 1939)

WHETHER animals are insusceptible to many of the nervous disorders which afflict man is not yet fully known, but there are many nervous disorders which either do not occur in animals or have not yet been described. A few of the diseases which might come into this category include certain of the congenital and hereditary ataxias, while the gliomata and neuro-vascular disorders appear to be extremely rare. On the other hand, encephalitis due to a neurotropic virus occurs in nearly all the domesticated animals, a study of which has undoubtedly augmented knowledge of the pathogenesis of virus encephalitis as a whole. It would seem, therefore, that studies in comparative pathology have not yet been fully exploited in the study of diseases the ætiology of which in man remains obscure. In the case of the demyelinating maladies much work has been done, but so far all attempts to solve the ætiology have failed. Many interesting hypotheses have been suggested, none of which has had subsequent satisfactory confirmation. On these grounds the identification of any parallel condition in animals would be of value, as the animals could be studied at various phases of the disease and experiments could be tried out on a large scale denied to the medical worker.

The object of this paper is to bring to the attention of the medical neurologist work which has been done in connection with a condition in lambs which has some similarity to certain of the demyelinating disorders in man. As a result of this work a new approach may be suggested towards solving at least the mechanism of demyelination. The results of this work have already appeared in veterinary journals ; this paper is a summarized account of all the work which has been done up to the present and incorporated in these papers. (Innes, 1936a, 1936b ; Innes and Shearer, 1939 ; Dunlop, Innes, Shearer, and Wells, 1939). It is written more or less in the chronological order in which the work progressed.

" Swayback " is one of a number of names which have been given to this disease of young lambs—probably by the farmers on account of the main

symptom of incoordination. While attention has only been directed to the disease recently, there is plausible evidence that it has existed in England for generations.

The disease affects newly born or very young lambs from apparently healthy mothers ; either sex, single lambs, both of twins, or even all three of triplets may be affected with no proclivity for any of these. Rarely only one of twin lambs is affected, but in many such cases the other lamb develops the disease later. In most outbreaks the majority of cases are affected at birth, but some do not show symptoms (or are not observed) until they are a few weeks old. Whether the lamb is born affected or not until later, the symptoms are essentially the same. All cases show incoordination ; some are totally unable to stand and lie helpless ; others may rise with difficulty to collapse immediately ; some may be able to walk with a straddled gait ; while the very mild cases show only a slight weakness of the hind limbs.

Although this ataxia is always definite, there is no flaccidity and spasticity may be marked ; fits are not observed, tremors are inconstant, and the few reflexes which can be tested are not exaggerated. Many of the severely affected animals are blind. The disease is non-febrile and is usually progressive except for the mild cases. Under natural conditions the mortality rate is high, death occurring either from secondary infection, from exposure and/or malnutrition. The very mild cases may survive, and are often bred from later to give birth to healthy lambs. Ewes of any age and of any breed appear to be prone to give birth to affected progeny, although there is some indication that older ewes or those which have been on affected land for more than one year are more prone.

In Britain the disease has a wide geographical distribution and occurs in most of the counties of England and Wales, a few of the Border counties of Scotland, and as far north as Caithness. The incidence, however, has been one of the puzzling features of the disease, for it varies for no apparent reason on the same farm from year to year and in different farms in the same district in the same year. On some farms it has occurred annually, to then cease, or again to occur on farms on which it had been previously unknown. In some areas, e.g. in North Derbyshire, Yorkshire, and near the Mendips, it occurs almost as an annual " enzootic " disease at lambing time, and outbreaks have occasionally been so severe as to compel farmers to give up sheep-breeding. In the Derbyshire area during the lambing of 1938 there was a 10 per cent. mortality of over 3,000 lambs born, but the mortality may on some farms be 90 per cent.

A similar disease seems to have occurred in S. America (Argentine and Patagonia), Sweden, India, South Africa, and New Zealand. Although the pathology of the disease in these localities was never investigated, it is highly probable from the general accounts given that the workers concerned were dealing with the same entity. An identical disease also occurs in Australia, where, however, the pathology established in this country has been subsequently confirmed.

The pathognomonic lesions are confined to the nervous system. Gross

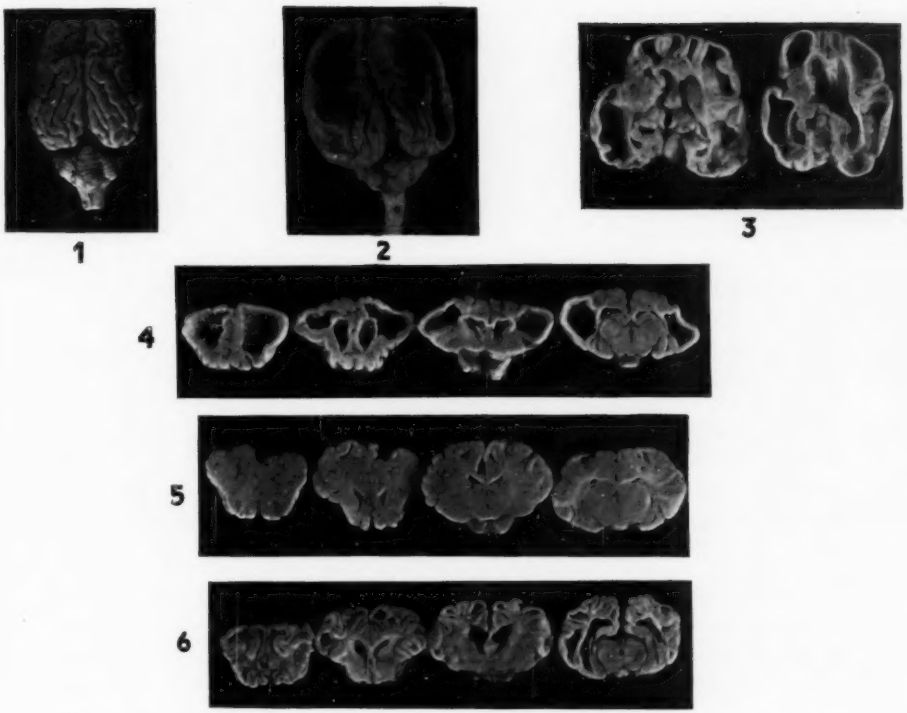


Fig. 1.—Brain, normal lamb ; superior aspect; for comparison with brains from Swayback cases ; the motor area in the superior frontal gyrus is shaded on the left side. About $\frac{1}{3}$ natural size.

Fig. 2.—Swayback: superior aspect of brain showing the collapsed appearance of the hemispheres after removal from the skull due to internal liquefaction and cavitation. Lamb; 3 days old; died. About $\frac{1}{2}$ natural size.

Fig. 3.—Swayback: horizontal sections of the cerebrum of two cases showing the gross destruction of white matter with extensive cavitation extending from the frontal to the occipital poles; the grey matter remains as a thin shell around the cavities. Left photo: lamb; 1 day old; died. The twin of this animal was still-born and showed no gross lesions in the brain. Right photo: lamb; 1 day old; killed. The twin of this case showed similar changes. About $\frac{1}{2}$ natural size.

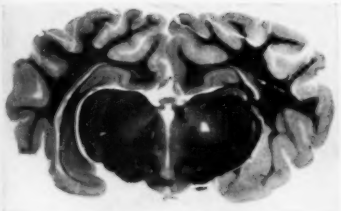
Fig. 4.—Swayback: coronal sections of the brain; extensive symmetrical degeneration of cerebral white matter with cavitation, wasting of corpus callosum and relative preservation of grey matter. Lamb; 5 days old ; died. About $\frac{1}{3}$ natural size.

Fig. 5.—Swayback ; coronal sections of the brain ; diffuse symmetrical gelatinous degeneration of the cerebral white matter; demarcation between grey and white matter blurred; no cavitation; the lesion here is reminiscent of that seen in Schilder's encephalitis. Lamb ; 6 days old ; killed. The twin of this case, also affected at birth, showed gross lesions similar to those seen in Fig. 6. About $\frac{1}{3}$ natural size.

Fig. 6.—Swayback: coronal sections of the brain; appearances seen might be regarded as a stage between that in Figs. 4 and 5 ; diffuse bilateral degeneration, rather gelatinous in the frontal poles, with liquefaction and beginning cavitation in the occipital region. Lamb ; 2 days old ; killed. About $\frac{1}{3}$ natural size.

changes are present in the brain in most cases, and those described below have been seen in lambs of ages varying from birth to a few weeks old and occasionally in still-born animals. The bones of the cranium are thin, but the sutures united, and when the skull is opened there is evident an excess of cerebrospinal fluid. The cerebral convolutions are ballooned out, and if cut or lacerated collapse like a severe hydrocephalus. The cerebral lesions are symmetrical and consist of a gelatinous degeneration of the white matter, or liquefaction is so extensive as to cause cavitation which may extend from the olfactory to the occipital poles. The transition between degeneration and cavitation may often be seen at different levels of the cerebrum. The white matter is thus restricted to a wasted *centrum ovale*, corpus callosum, and capsules, while the cortex simply forms a thin shell of matter around the degenerated areas. In cases seen at an earlier stage cavitation may not be marked and the diffuse bilateral gelatinous degeneration is highly reminiscent of the lesions in Schilder's encephalitis. In this latter type the brain is soft and flabby, the convolutions rather blurred, and the demarcation between grey and white matter not clearly distinguished. The process has some predilection for the occipital poles and spreads anteriorly. Occasionally a secondary ventricular dilatation may be present, but macroscopic lesions are not found in the mid-brain, cerebellum, brain stem, cord, choroid plexus, and meninges. In a number of lambs showing only slight symptoms gross changes may not be found.

Histologically, demyelination is the constant and probably the primary lesion, the most severe type being represented by an almost total loss of cerebral myelin, affecting all zones in a diffuse manner. In a series of cases all gradations are seen, ranging from this severe type to small symmetrical foci of demyelination often present, for example, in those cases which showed no gross changes. Where liquefaction had been extensive the white matter was restricted only to a thin subcortical layer forming a margin to a cavity. The demyelination process seems to occur in a singularly rapid manner, as accumulations of stainable lipoid, although frequently seen, are never present in gross amounts. Consequently it is not surprising that focal or perivascular collections of amœboid phagocytic glia are not a conspicuous feature of the lesion. Nissl or hæmatoxylin preparations show all gradations in these different cases, ranging from an apparently normal white matter to that of extreme *status spongiosus*. No gross patches of demyelination are found in the lower levels of the brain, but two well-defined nerve-fibre tracts in the cord are affected by a descending degeneration. These tracts are present (*a*) in the ventral column applied close to the median fissure and (*b*) forming another compact group in the dorso-lateral column close to the tip of the dorsal horn of grey matter. They correspond closely to the motor tracts which have been demonstrated in the sheep by experimental hemisection lesions, and probably represent combined pyramidal and rubro-spinal tract degeneration. The relative resistance of the nerve cells in all parts of the system form a conspicuous feature of the pathology. Pyknotic changes may occasionally be seen in the cells of the motor cortex and chromatolytic changes constantly in the cells of the red nucleus. Gliosis is easily demonstrable by suitable methods, although it is not so pronounced as



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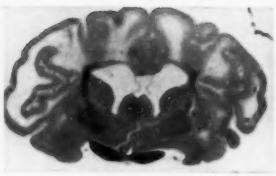

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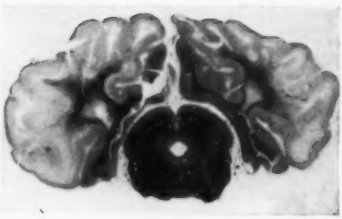

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Fig. 7.—Normal lamb: coronal section of brain; Weigert-Pal. Compare with Swayback cases, Figs. 8 and 9. About natural size.

Fig. 8.—Swayback: diffuse bilateral demyelination to the extent of almost total loss of myelin with the exception of the optic chiasma. Lamb; 2 days old. About natural size.

Fig. 9.—Swayback: three-weeks-old lamb; diffuse bilateral demyelination of the hemispheres affecting particularly the subcortical zones; the fibres deep in the *centrum ovale* remain densely stained. About natural size.

Fig. 10.—Swayback: cornal section from frontal lobe near motor area, corpus callosum and ventricle below; diffuse demyelination most severe at the summits of the convolutions. Lamb; 11 days old; died. × 4.

in comparable human maladies. It is necessary to emphasize : (*a*) that infiltrations by cells which are known to follow recognizable inflammatory agents in the nervous system are never found ; (*b*) that neuronophagia is never seen ; and (*c*) that a search for inclusion bodies failed.

The lesions thus offered a picture of a pathological entity which had hitherto not been described in domestic animals. Several conclusions were made at this time subsequent to the establishment of the pathology and there have been no fresh observations made to cause these to be altered. These are as follows:

1. The disease is one of a primary ante-natal origin.

2. The destruction of the cerebral myelin can only be regarded as an idiopathic disintegration of a substance which had been already formed *in utero*, the process is thus a true demyelination and not a myelin aplasia.

3. The state of myelination at the time the causative agent begins to operate must be an influential factor on the genesis of the disease. In this connection it must be obvious that the process does not begin until a relatively late stage of gestation, otherwise a greater degree of brain deformity than that seen would result.

4. While the history and pathology of many cases indicate that the disease is acute and progressive in nature, there is also a milder non-progressive type ; animals in the latter category survive to give birth to healthy progeny later.

5. In the mild type the causative agent must have then a minimal tempo of action or comes into action at a time late in gestation when only a small amount of myelin damage can take place. The cause is not operative beyond this period in fœtal life as far as transference from the ewe is concerned, as it is a common practice to suckle healthy lambs on to ewes which have lost their lambs from " swayback " ; such foster lambs never develop the disease.

6. The tendency to early liquefaction of the cerebral lesions must be regarded as an exaggerated parallel to the difference in reaction between the brain of the child and adult to tissue destruction.

7. " Swayback " as a consequence has a number of features which are reasonably comparable to Schilder's encephalitis in the human, bearing in mind the possible differences in reaction which must almost necessarily occur in the lamb compared with a child. If Schilder's disease is only to be regarded as an anatomical entity the resemblance must be very close.

Ætiology

The failure which has attended attempts to solve the ætiology of the demyelination diseases of man rendered the prospect of success with this lamb condition a gloomy one. The disease showed so many puzzling features that it is not surprising now to note how the work took the simple course of the elimination of known causal disease factors. All attempts to isolate either a causal organism or virus either by cultural work or transmission experiments failed ; this negative result is of importance in view of the parallel negative ones which have been obtained repeatedly in connection with the demyelination diseases of man and monkey. Similarly, no evidence could be obtained to incriminate either breeding or hereditary factors, and it was soon apparent that deficiencies of any of the recognized vitamins or the more common minerals could also be eliminated as possible ætiological factors.

One other possible cause remained at that time as an obvious and necessary course of investigation ; this concerned the incrimination of lead in " swayback."

Lead-Poisoning and " Swayback "

The association of lead with certain of the demyelination disorders of man has often been suggested. It is not without interest, therefore, that a similar cause was assigned to " swayback " from several different sources.

In certain areas in England, e.g. in Derbyshire, it is an old belief of the farmers that " swayback " is a form of plumbism and a common name for the disease in this county is " belland." (The latter term originally meant in lead-mining areas the fine dust of lead ore ; as a consequence of the highly poisonous nature of the latter, the same term was applied to lead poisoning ; land which is known to contain large amounts of lead is thus often referred to as " bellanded.") Many of the fields in this area are irregularly traversed with what are known locally as " lead rakes "—remains of old lead mines—which have in course of time been overgrown with grass to which grazing animals have free access. The presence of lead in the soil and grass is said to give the latter a sweetish taste and animals eat it readily. Instances of " belland " in other animals (mainly horses and poultry) in which a paralysis of the hind limbs occurs are quoted by the farmer in support of his belief ; but the pathology of these cases has never been accurately determined. Independent observations in Australia also indicated that lead might be involved in the ætiology, as workers there found quantities of the metal in " affected " ewes' milk. As a result deleading experiments were made by the administration of ammonium chloride to pregnant ewes on affected land, with an apparent reduction of the disease in the progeny. In the absence of other proof at that time the position regarding lead as a cause was, however, very uncertain. From these observations it was obvious that lead could not be dismissed cursorily as of no moment, in

spite of the fact that " swayback " was not apparently confined to districts where lead outcrops are known.

Chemical analyses showed an extremely high lead content in the grass of many of the " affected " farms in the Derbyshire area and the livers of cases of swayback and their mothers contained lead in amounts which had to be considered highly abnormal. The difficulty, however, lay in the interpretation of the exact significance of these findings in the light of what was known about the disease. The ewes, for example, never at any time show signs of grave ill-health and certainly not of plumbism. Consequently it had to be considered that if lead was involved the ewes must ingest lead insidiously over a period of years and that for some reason the metal only affects the brain of the developing lamb. In view of Aub's work there are, of course, no great obstacles in the way of finding an explanation for this transient liberation of lead from the ewe's tissues during pregnancy and its transport through the placenta. It was, however, another matter to attempt to prove this experimentally.

From the pathological point of view there were no lesions present either in the ewes or the lambs diagnostic of plumbism. The lead line in the gums was only occasionally seen ; an anæmia with punctate basophilia was not a constant feature ; while X-ray examination of the bones showed nothing similar to the lead line in human lead poisoning. The cerebral lesions were of no diagnostic help, as there are no data available to indicate the appearances of lead encephalopathy in lambs.

The position at present is that until we know more about the exact ætiology of " swayback," lead cannot be ignored as a possible complicating causative factor. " Swayback " need not be, and in fact cannot be, a direct form of plumbism. But we do not know how the presence of lead in the diet might affect the assimilation of other substances, or when present in the body tissues how it might affect normal myelin metabolism. The urgent need at the moment would seem to be the establishment of more exact criteria which would enable the recognition of the early ætiological connection between lead and injuries to the animal organism.

Copper Deficiency and " Swayback "

The idea that a " trace element," such as copper, might be associated with the disease no doubt took origin from observations in a field divergent from that of nervous disorders, namely, the discovery of cobalt as a factor in controlling certain nutritional anæmias in sheep in Australia. This suggestion of a copper deficiency arose from work by Bennetts (1937) in W. Australia. Twelve pregnant ewes on " affected " land were given periodic doses of copper sulphate during pregnancy ; their lambs failed to develop " swayback," while in the control group receiving no copper the incidence was 100 per cent. The conclusions of this work were as follows :—pregnant ewes pastured on" affected " land developed a macrocytic hyperchromic anæmia, and as a result their lambs were affected with " swayback." The copper content of the blood, liver, and

milk of these anæmic ewes was much below normal. The feeding of copper caused a marked response in the blood picture, the anæmia was thus cured and the progeny were not affected with " swayback." This anæmia was considered to be analogous to pernicious anæmia, although it did not respond to liver therapy. A few analyses of the grass showed that there was no copper deficiency present and the pathogenesis awaited further explanation.

Copper has for long been known to play some part in normal erythropœisis, although its exact rôle is still unknown. This was, however, the first time that any suggestion had been made regarding a vital connection between a " trace element " and myelin.

In 1938 investigations were begun along these lines which ultimately involved much hæmatological and chemical work and finally a large-scale field experiment to determine more accurately the prophylactic value of copper in " swayback."

Hæmatological examinations of many ewes in " swayback " areas compared with suitable control animals showed that while an anæmia was occasionally present in ewes which gave birth to " swayback " lambs, it was not constantly related to the disease of the progeny. An anæmia was found in ewes which also gave birth to healthy lambs in and away from affected " swayback " areas. Also no evidence was obtained to show that this anæmia was macrocytic and hyperchromic in type ; macrocytosis, evident from a series of Price-Jones' curves, was undoubtedly absent and there was no evidence to show that the anæmia was even hyperchromic. It was concluded that the observations of Barcroft regarding the occurrence of a raised blood volume and decreased hæmatocrit reading in normal pregnant ewes might indeed indicate that this " anæmia ", which we found, could be partly explained on this physiological basis. There was similarly no uniform change in the blood picture of " swayback " lambs.

Chemical analyses showed that the copper content of both the blood and liver from " swayback " cases was much lower than that of normal lambs of the same age and that the copper content of the ewe's blood was likewise low. Although not constant there also seemed to be a relationship between the blood Cu of the affected lamb and its mother. At the same time there was the puzzling feature that the Cu content of the blood of ewes (as a whole) in the Derbyshire area was much lower than that in ewes from a control area and in some cases was of the same low magnitude as in ewes which gave birth to " swayback " lambs. Grass analyses showed that there was no Cu deficiency present.

A field experiment was carried out in the centre of a " swayback " area on Bradwell Moor, Derbyshire. Ewes were obtained on loan from farmers in this district to act as our experimental flock, while the experimental area consisted of 300 acres which had been divided off into four separate but contiguous enclosures ; another field about a mile away acted as an additional control area. All the ewes were numbered for identification purposes and divided into control and experimental groups. One control group was kept in this main experimental area, while the other control group was kept in the isolated enclosure. The experimental groups comprised two main flocks of animals

which received during pregnancy pure salt licks containing 0·3 per cent. and 1 per cent. Cu (as $CuSO_4$) respectively ; animals from these two flocks were drafted on to this lick treatment at various times during pregnancy, from 23rd of December, 1938, 11th January, 1st March, 23rd March, 1939. (The gestation period in the sheep is about 21 weeks, lambing beginning in this area about the middle end of March, so that this meant the ewes would be receiving treatment for roughly 12, 10, 7, and 4 weeks before parturition.) The animals were moved around the four enclosures in the area every three weeks, so that all ewes received virtually the same treatment. The results of this feeding experiment are shown in tabular form below.

NUMBER OF LAMBING EWES, BIRTHS, DEATHS, AND CASES OF " SWAYBACK " IN THE VARIOUS GROUPS.

GROUP.	NUMBER OF EWES.*	NUMBER OF LAMBS BORN.	NUMBER OF LAMBS DIED.	CASES OF " SWAYBACK."†	DEATHS FROM ALL OTHER CAUSES.‡	NUMBER OF EWES WITH "SWAYBACK" LAMBS.
Control A ..	40	63	40	24 (1)	18	16
Control B ..	40	60	28	12 (2)	17	10
Total	80	123	68	36	35	26
Experimental C. 1 per cent. Cu from						
23rd Dec. ..	15	27	7	0	7	0
11th Jan. ..	10	16	4	0	4	0
1st Feb. ..	11	17	5	1	4	1
23rd Feb. ..	10	17	4	1	3	1
Total	46	77	20	2	18	2
D. 0·3 per cent. Cu from						
23rd Dec ..	32	50	20	0	20	0
11th Jan. .	15	20	3	1	2	1
1st Feb. ..	16	25	7	4	3	3
23rd Feb. ..	18	28	13	8 (3)	6	6
Total	81	123	43	13	31	10

* The numbers in this column are less than the original number placed in these groups at the beginning of the experiment owing to deaths, barren ewes, and animals which were missing at the final identification. There was no evidence whatsoever that the mortality in the ewes was due to the copper treatment ; the causes of death included obvious infection, pneumonia, one case of cirrhosis, and deaths during parturition from obstetrical troubles.

† The cases of " swayback " include a few animals which showed symptoms shortly after birth and which were not killed. (1) two cases ; (2) one case ; (3) one case.

‡ This includes still-born lambs.

It will be seen that the incidence of " swayback " is highest in the control group (A) which had been kept away from the main experimental area and slightly lower in the other control group. Compared with this incidence, the absence of cases of the disease in the experimental groups which received either 0·3 per cent. or 1 per cent. Cu lick from 23rd December, 1938, until lambing is striking and convincing proof of the efficacy of copper in the prevention of the disease. The incidence increased accordingly as copper treatment was delayed, so that in the group which received Cu licks for only a short time before lambing (from 23rd March, 1939) there is little difference in the number of " swayback " lambs to that of one of the control groups (B).

These results are of significance, although we cannot offer at this stage any explanation of the mode of action of copper and from this of the pathogenesis of the disease. The disease is not one of a Cu deficiency *per se* in the ewe, as analyses of the herbage showed no difference in the Cu content compared with control pastures. It might therefore be simply a hazard to speculate at this stage, but there are some explanations which may be tentatively offered : (*a*) A depletion of Cu reserves in the ewe takes place before the birth of an affected lamb ; this is reflected in a reduction of the Cu stores of the newly born " swayback " lamb compared with a normal one. (*b*) The level of Cu in the blood of the ewe is not the primary factor which determines the development of " swayback " in the lamb, as low levels are sometimes found in ewes on the same farm which give birth to healthy progeny. (*c*) The Cu deficiency might therefore be a relative one which could be explained either by the element being present in an unsuitable form in the grass or by the presence of some other factor in grass which would inhibit the absorption of Cu or by the presence of alimentary dysfunction in the ewe inhibiting the Cu gut absorption and/or an increased rate of excretion of Cu in the ewe.

The ætiology of this demyelinating disorder in lambs can thus be regarded in a new light, although much work will still be necessary to determine the exact physiological rôle of copper in relation to myelin metabolism. No suggestion is made that other demyelination diseases have a similar causal foundation, as it is highly probable that the problems asssociated with them are several and not one and that the demyelination lesion is only the limited reaction of the nervous system to a number of factors. The work does, however, suggest a method for a more intimate study of the mechanism underlying the process of demyelination.

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A CRITICAL REVIEW

VITAMIN B DEFICIENCY AND NERVOUS DISEASE*

BY

C. D. ARING and T. D. SPIES

AFFECTIONS of the nervous system which result from inadequate nutrition have assumed an increasingly important position through the rapid accumulation of clinical, experimental, and pathological data. The artificial synthesis of a number of the components of the vitamin B complex has made available pure crystalline material in large amounts for clinical research, and thus a milestone in the history of these affections has been passed. It now seems appropriate to review and summarize the knowledge of these important substances.

To evaluate the status of a nutritional deficiency in man is difficult. As a rule the patient induces his own disease and provides a deficiency that is not quantitatively measurable, but frequently clinical and laboratory evaluations are attempted. Both the laboratory method and the clinical method have certain advantages. Mice are not yet men and until they are the work coming from the study of human beings is essential. Since the experience of investigators working with animals may often point the way for clinical research, we have interspersed in this review a few of the pertinent studies on the effect of nutritional deficiency on the nervous system of animals.

A scheme for illustrating the multiple factors of the vitamin B complex is given in Fig. 1. To date the following portions of the vitamin B complex have been isolated and synthesized in amounts sufficient to allow for clinical trial : thiamin hydrochloride, nicotinic acid, riboflavin, and 2-methyl, 3-hydroxy, 4, 5-di (hydroxymethyl) pyridine. The deficiencies of these substances as they apply to the nervous system of man will be discussed briefly.

Method of study

Methods of control in the clinical study of the nutritional deficiencies are possibly the explanation for the varying results obtained in the treatment of these diseases from clinic to clinic and from physician to physician. Briefly our method has been to place under observation any patient suffering from nutritional deficiency immediately after admittance to the hospital or clinic. The history and physical examinations usually are sufficient to make the

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diagnosis. Borderline cases or those of the subclinical variety are not selected for clinical study unless the patient is a remission from a previous attack. We have found that certain objective laboratory tests are useful and reliable indices of specific deficiency states. Since disturbance in porphyrin metabolism is

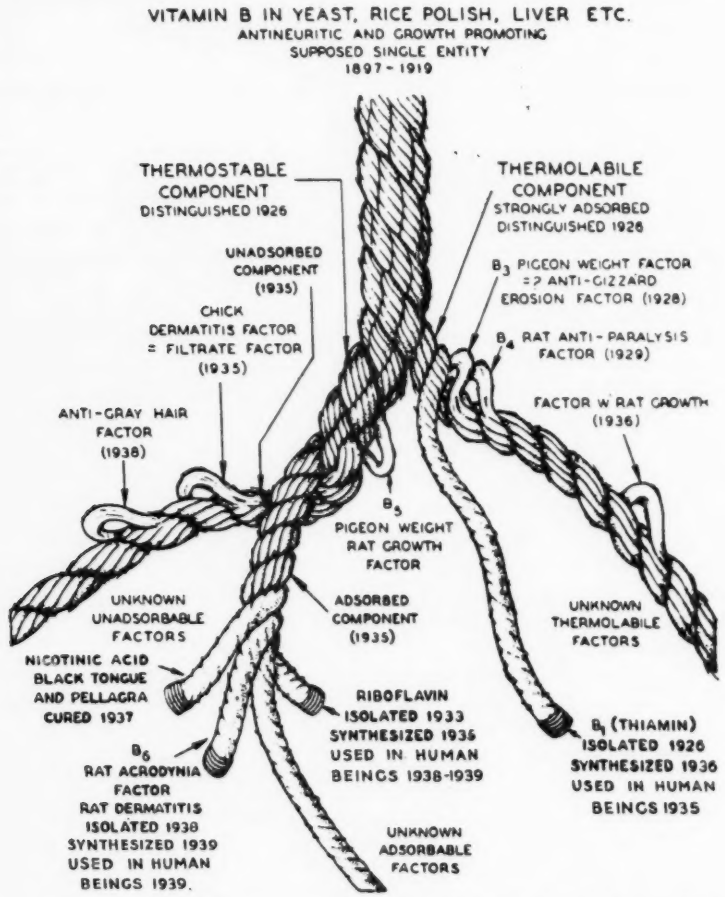
VITAMIN B IN YEAST, RICE POLISH, LIVER ETC.
ANTINEURITIC AND GROWTH PROMOTING
SUPPOSED SINGLE ENTITY
1897 - 1919
THERMOSTABLE COMPONENT DISTINGUISHED 1926
THERMOLABILE COMPONENT STRONGLY ADSORBED DISTINGUISHED 1926
UNADSORBED COMPONENT (1935)
CHICK DERMATITIS FACTOR = FILTRATE FACTOR (1935)
B_3 PIGEON WEIGHT FACTOR = ? ANTI-GIZZARD EROSION FACTOR (1928)
B_4 RAT ANTI-PARALYSIS FACTOR (1929)
FACTOR W RAT GROWTH (1936)
ANTI-GRAY HAIR FACTOR (1938)
B_5 PIGEON WEIGHT RAT GROWTH FACTOR
UNKNOWN UNADSORBABLE FACTORS
ADSORBED COMPONENT (1935)
UNKNOWN THERMOLABILE FACTORS
NICOTINIC ACID BLACK TONGUE AND PELLAGRA CURED 1937
RIBOFLAVIN ISOLATED 1933 SYNTHESIZED 1935 USED IN HUMAN BEINGS 1938-1939
B_1 (THIAMIN) ISOLATED 1926 SYNTHESIZED 1936 USED IN HUMAN BEINGS 1935
B_6 RAT ACRODYNIA FACTOR RAT DERMATITIS ISOLATED 1938 SYNTHESIZED 1939 USED IN HUMAN BEINGS 1939.
UNKNOWN ADSORBABLE FACTORS

Fig. 1.—Differentiation of the components of Vitamin B complex. The components that have been isolated in a pure state are indicated in heavy lettering ; those which have been recognized only by the discrepancies in physiological properties of various crude extracts are indicated as loops ; the possible still unknown factors are divided into three main strands according to the principle of adsorbability which has been so useful in differentiation experiments.

often an important part of the deficiency syndromes, the urine of each patient is examined to determine the excretion of porphyrin or other ether-soluble red pigments which can be extracted in 25 per cent. HCl. Using a bacteriological method, determinations are made of the concentration in the body fluids of

cozymase, an enzyme fundamental to cellular respiration ; the blood and urine of pellagrins contain only a fraction of the normal concentration of this enzyme. Studies are also made of the urinary excretion of vitamin B1, and a decreased output is suggestive of both beriberi and pellagra. The progress of symptoms over a period of days is noted while the patient is maintained, without therapy, on a restricted diet or on the identical diet that produced the deficiency. A rigid check is made of the dietary of all patients entering the Nutrition Clinic of the Hillman Hospital, Birmingham.

If no improvement in the symptoms of the nutritional deficiencies occurs under these conditions, they serve as an index for testing the potency of therapeutic agents. A specific therapeutic agent is of value if the symptoms of the deficiency clear promptly in all cases when sufficient amounts of the pure substance are added as a supplement to the control diet, all other conditions remaining constant.

It is probably superfluous to add that in the clinical study of the patients with nutritional deficiencies it is advisable to use only one therapeutic agent at a time. Another point to be considered is the fact that the patient may be improved by merely resting in bed.

To avoid the benefit of suggestion as much as possible, we substitute similarly appearing medicaments for the specific substance and observe the result.

Vitamin B1 (thiamin, aneurin, catorulin) deficiency

It is generally agreed that a prolonged deficiency of vitamin B1 in man may result in peripheral neuritis. By the term " neuritis " is meant disease of the neurone (Brown, 1938). The principal causes of neuritis may be grouped under six inclusive headings, as has been done by Cobb and Coggeshall (1934). As the ætiological agents causing neuritis are better understood, such clinical classifications will be replaced by classifications based solely on ætiology. Although this classification is arbitrary and imperfect as a result of the present state of our inadequate knowledge, it simplifies the understanding of the problem of neuritis. The types of neuritis as noted by Cobb and Coggeshall will be considered, and information and experience in the therapy of these diseases with vitamin B1 will be noted. In the table, peripheral neuritis has been divided into local and general, and in this manner the unilateral disorders affecting one nerve are segregated from the large group of systemic disorders which cause multiple neuritis.

Localized Neuritis

Mechanical	*Infections*
Pressure	Diphtheria
tumour	Tetanus
œdema	Streptococci
arthritis	Leprosy
fibrosis	
Trauma	
Saturday-night paralysis	
Volkman contracture	
Meralgia paresthetica	

Localized neuritis usually occurs in ambulatory patients, and mechanical or infectious ætiological agents can be determined by clinical methods. The symptoms usually respond to medical and surgical therapy. Relief of localized neuritis following the administration of crystalline vitamin B1 has been reported by some investigators. Such reports, however, tend to be misleading, since physicians who obtain negative results are not prone to report them. Furthermore, the number of cases which have been reported is small and, in general, the studies are not adequately controlled. Hence the results need confirmation. Our unfinished studies show that some cases are relieved by thiamin and others are not. No conclusive reports have as yet appeared in the literature establishing the value of vitamin B1 in the prevention of localized neuritis.

We have observed the relief of the acute pain following the use of vitamin B1 in a case of brachial neuritis which developed six weeks after mastectomy. This case report is given because the results of the vitamin therapy of apparently similar cases are so confusing and the experiences of various men contradictory.

A female, age 44, on 13th September, 1938, had a simple mastectomy under cyclopropane anæsthesia, for chronic cystic mastitis, at the Cincinnati General Hospital. Twelve hours after the operation there was pain in the arm on the same side ; this arm had been strapped to the side of the patient during the operation. The extremity felt heavy until six weeks later, when the patient awoke one morning with severe pain in the arm (after taking a long automobile trip during which she had done no driving). There was numbness of the first and second fingers and weakness of the entire extremity. All symptoms were aggravated by use of the extremity, and were worse at night.

The patient was examined by one of us on 4th December, 1938, $2\frac{1}{2}$ months after the operation. The pain which had been present constantly was not relieved by analgesics. There was no history of obvious dietary deficiency, although she had lost her appetite and had vomited occasionally after the onset of the acute pain. She had lost 15 lb. in weight since the operation.

Neurological examination revealed atrophy of the musculature of the forearm. All movements of the affected extremity were reduced in speed and volume. She complained of continuous numbness and tingling of the hand and fingers. Manipulation of any of the muscles of the extremity caused pain. Pressure in the axilla or in the supra-clavicular space caused great pain. The trapezius muscle on the same side was tender. The only demonstrable loss of sensation was that to light touch in the skin of the distal joints of the fingers and thumb on the affected side. The tendon reflexes were normal.

An injection of 50 mg. of thiamin hydrochloride was given intravenously in sterile physiological solution of sodium chloride daily for three days. She slept well on the first night after the medication, whereas previously she had been unable to rest despite large doses of codeine, emperin, nembutal, bellergal, or sodium phenobarbital. All sedatives and analgesics were discontinued after the third injection, and the patient was then allowed to go three days without thiamin. On the third day, the constant aching pain had returned, but again was relieved by the intravenous injection of 50 mg. of thiamin hydrochloride. This dosage was repeated daily until a total of 350 mg. had been given. The movements of the extremity became stronger, although not as strong as those of the unaffected extremity. She had occasional mild pain as long as 5 months after the onset, but it was not severe enough to require analgesics or intravenous vitamin B1 after the seventh injection. She continued to improve, and 8 months after the onset had practically recovered.

The criteria at our command led us to classify this patient as a case of localized mechanical neuritis. The result obtained with thiamin was prompt and satisfactory. In fact, the patient was uncomfortable with medicaments other than thiamin. Cases such as this illustrate our incomplete knowledge of this subject, and a reasonable explanation of their physiological pathology cannot be given with the data at hand.

Generalized Polyneuritis

Virus

Measles	" Landry's "
Small pox	Poliomyelitis
Chickenpox	Encephalomyelitis
Parotitis	Epidemic (lethargic) encephalitis
Herpes	Erythro-edema
Acute febrile (infectious or infective)	Acute rabic myelitis

The virus diseases listed above are often characterized or accompanied by peripheral neuritis as a late complication. No crucial observations have been made to determine whether faulty nutrition plays a role in the development of the neuritis seen in these diseases. The evidence available tends to show that vitamin B1 does not play any direct role in counteracting the effects of these infectious agents.

Our experience with three cases of infectious polyneuritis has been that they have had progression of some of their neurological signs despite large doses (50 mg. twice a day) of thiamin intravenously. In two of these cases this therapy was continued for 1 month.

Bacteriotoxic

Focal infections	Typhoid fever
" Rheumatism "	Paratyphoid fever
Erysipelas	Typhus fever
Scarlet fever	Influenza
Rheumatic fever	Pneumonia
Chorea	Malaria
Septicæmia	Relapsing fever
Puerperal fever	Serum sickness
Gonorrhœa	Acute enteric fever
Meningitis	Syphilis
Diphtheria	

The diseases in this group often interfere with proper nutrition and thus predispose the patient to development of a deficiency of vitamins. Many patients with infection also have an increased requirement for certain essential nutritive substances. In typhoid fever, for example, the requirement for vitamin B1 is raised because of the high fever, loss of appetite, or excessive diarrhœa. The incidence of peripheral neuritis in patients with typhoid fever was high a few decades ago, when an effort was made to restrict the diets of such patients. The great decrease in the incidence of peripheral neuritis in typhoid fever in recent years is probably due to the prescription of adequate diets in the treatment of that disease. In fact, it is becoming uncommon to see neuritis incident to the bacteriotoxic diseases, probably because of the increasing awareness of the importance of proper nutrition in the ill. We have little

information concerning the role of vitamin B1 deficiency in the development of any of the neuritides accompanying bacteriotoxic diseases, but a number of reports have appeared indicating that the administration of vitamin B1 often relieves the symptoms of neuritis in these cases. The neuritis of acrodynia possibly belongs under this heading. Durand, Spickard, and Burgess (1939) reported the cure of acrodynia in two children following the intramuscular injections of vitamin B1.

Chemical

Mercury	Triorthocresyl phosphate
Lead	Aniline
Silver	Sulphonethylmethane barbital, etc.
Arsenic	Chloral, chlorbutanol
Phosphorus	Carbon monoxide
Methyl alcohol	Carbon bisulphide
Ethyl alcohol	Thallium
Ethyl iodide	Sulphur
Trichlorethylene	Emetin
Carbon tetrachloride	Gold
Trinitrotoluene	Bismuth
Dinitrobenzene	Sulfanilamide

The course of two cases of triorthocresyl phosphate poisoning (Jamaica ginger paralysis) two weeks after the onset of symptoms was unaltered by the use of large amounts of crystalline vitamin B1 * by mouth. One of the patients received 20 mg. daily for a period of 1 month and the other received 500 mg. daily for the same length of time. The symptoms of neuritis progressed despite this therapy, and signs of involvement of the pyramidal tracts became obvious within 3 weeks after the onset of the neuritis. It is theoretically possible that large amounts of vitamin B1 crystals given before the ingestion of triorthocresyl phosphate might act as a protective agent. It has been reported that the administration of vitamin B1 causes relief of the symptoms of the neuritis following exposure to toxic agents such as nicotine, lead, thallium, arsenic, and mercury. As yet, however, there is no conclusive evidence that the lack of vitamin B1 plays a major role in the development of any of the "chemical neuritides."

A case report is appended to illustrate the improvement that may be obtained in neuritis considered to be of chemical origin.

A man of 40 had experienced the onset of diarrhœa in mid-May of 1938, which was continuous through August 1938. Despite the daily occurrence of diarrhœa, which was accompanied by some cramping of the abdomen, the patient remained at hard work every day during this period. Repeated stool examinations were negative, but despite this a thorough course of emetine was begun in August as the patient was suspected of having amœbic dysentery. It is thought that about $\frac{3}{4}$ grain was taken by injection at a single dose and there had been 10 doses. The diarrhœa ceased after the first dose of emetine. In early September he was able to get away from work for two weeks. On returning from this holiday, he observed the occurrence of a peculiar stinging in the inner surface of the sole of the left foot. This paresthesia ascended the foot in a rather indefinite manner, following no nerve or segment distribution. Shortly after the occurrence of this numbness and paresthesia in the left foot, he observed the same thing in the right foot and the peculiar sensation ascended the left leg and finally

* Furnished through the courtesy of Merck and Company.

involved all of both legs and a portion of the lower thigh. There had also been some numbness about the left hip. There had been no difficulty whatsoever with the upper extremities or about the head and face. He described the sensation as diminished sensation in the lower extremities (feeling as though the feet had been asleep and were just coming out of this state). He stated that there was no complete loss of sensation anywhere. Underneath this sensory loss there was a dull aching which went unnoticed if he concentrated on some other subject. The lower extremities felt better if he shifted their position rather frequently when sitting. If he walked as far as 400 yards he noticed that the aching became more obvious and his legs tired. There had been no bladder disturbance. There was no stiffness in the extremities. He believed that the motor power was good and near normal in the lower extremities. His gait was no different than before the onset of difficulty in his lower extremities.

It is important to note that the food intake had been considered to be good throughout the illness, that is, since May and before, and that the beginning of his neurological symptoms occurred just about two weeks after the last injection of emetine.

Neurological examination was performed on 25th October, 1938.

Cranial Nerves.—Movements of the eyes were full in all directions ; there was no nystagmus. Sensation of the face was normal throughout. Movements of the jaws and face were normal. Movements of the neck were strong to either side. The tongue protruded in the midline.

Motor System.—There was no loss of motor power in any of the extremities. Tone was normal and muscle development was excellent throughout. The gait was essentially normal. He walked on a rather broad base and his toes pointed outward, but he walked well, raising his feet properly. He did not have to watch his feet.

Sensory System.—There was slight tenderness to deep pressure over the nerve trunks and in the muscles of the legs, especially the calf muscles. Sensation in the upper extremities, including the appreciation of vibration, was normal with the exception of slight diminution of pain and touch in the distal two joints of all of the fingers. In the lower extremities there was loss of sensation in the lumbar segments below the mid-thigh. This was not a complete loss, and sensation improved in an ascending manner. The appreciation of temperature, pain, and touch was similarly affected. There was hyperæsthesia of the first and second sacral segments in the lower extremities. The appreciation of vibration was almost completely absent in the lower extremities below and including the patellas. The appreciation of passive changes in position of the toes was very good. Tendon reflexes in all of the extremities were normally active. There was no clonus. An occasional response on testing for a right Gordon was obtained which was as follows : the right great toe dorsi-flexed slightly without any fanning of the other toes. The other plantar responses were " flexor " in type.

The excellent and detailed history which this patient gave suggested that the cause of the neuritis was emetine rather than nutritional deficiency. The patient had an excellent appetite throughout his illness. His food intake was exceptionally good, and the diarrhœa had remitted two weeks before the onset of the neuritis, when he was on a holiday and apparently in good health.

Treatment with vitamin B1 was begun five weeks after the onset of the neuritis ; 100 mg. of thiamin was given intravenously twice daily. Beginning of relief occurred within 12 hours after the first injection. This dosage was maintained for 3 days with great relief of the paresthesias, aching, and fatigue. Thiamin was then administered by mouth in amounts of from 100 to 500 mg. daily for three weeks. For two days at the end of this period, when the patient was taking these large amounts of thiamin by mouth, he was given a supplementary injection of 100 mg. intravenously twice per day. He noted that he

received additional benefit from the intravenous injection and that the oral administration of vitamin B1 could not compare in its effect to that obtained from the intravenous administration. Thiamin was continued by mouth until the patient had had three months of treatment, at the end of which time he was completely relieved of symptoms.

We have been unsuccessful in treating the neuritis in the upper extremities of a young man, a worker with refrigerants. Repeated large intravenous injections of vitamin B1 had no effect on the course of the neuritis, which was probably due to methyl chloride.

Nutritional Deficiency or Metabolism

Pellagra	Cancer with cachexia
Pernicious anemia	Tuberculosis with cachexia
Sprue	Senility with cachexia
Beriberi	Diabetes
" Alcoholic neuritis "	Myxedema
" Korsakoff's psychosis "	Hematoporphyrinuria
Pernicious vomiting	" Recurrent polyneuritis "
Hunger œdema	" Chronic progressive polyneuritis "
Pregnancy	Chronic bacillary dysentery
Chronic colitis	

There is a long list of diseases in which polyneuritis, when it occurs, is directly related to the lack of proper nutrition. This list is composed chiefly of metabolic and deficiency diseases which often have a number of clinical features in common. In the scope of this article we are concerned chiefly with the neuritic manifestations which may affect patients having any of these diseases.

Evidence is accumulating which indicates that many of the neuritic symptoms listed under various syndromes are clinical variations of one large ætiological group. Since vitamin B1 will prevent and usually relieve the manifestations of the polyneuritis of beriberi, a known dietary deficiency disease, and since it is essential for the integrity of the nervous tissue in general, it seems likely that its absence may play a very important part in the development of neuritis in a number of these diseases in addition to beriberi. Evidence indicates that vitamin B1 is a useful therapeutic agent in the treatment of " alcoholic " neuritis, with or without pellagra, polyneuritis of pregnancy, and the neuritis of diabetes. Most of the other diseases under this heading are related to disturbances of nutrition, and it may well be that a lack of vitamin B1 plays a role in the production of the neuritic manifestations which so frequently accompany them. These diseases of metabolism are often associated with loss of appetite and malabsorption, conditions which, in themselves, may lead to a deficiency of some specific factor or factors.

The clinical manifestations of these diseases are extremely variable. Studies of a large group of people who are addicted to alcohol and who are also malnourished show that some individuals have no symptoms ; that some have symptoms of beriberi ; and that others have nervous, dermal, and gastrointestinal changes characteristic of pellagra. Still others will show hæmatological and neurological changes similar to those associated with sprue and pernicious anæmia. Some of the persons addicted to alcohol develop Korsakoff's syndrome. This clinical syndrome is characterized by a peripheral

neuritis which is identical with that of beriberi and by a psychosis often resembling the mental changes seen in pellagra.

PELLAGRA.—The pellagra syndrome conspiciously affects the alimentary tract and the dermal and nervous systems. The symptoms arising from involvement of the nervous system, like the other symptoms of pellagra, do not appear in any regular order. They arise from cerebral involvement, degeneration of the spinal cord, and peripheral neuritis. The mental changes may be clinically identical with those of Korsakoff's psychosis, or in fact the symptoms may manifest themselves as any of the well-known psychotic types. The peripheral neuritis is clinically indistinguishable from the polyneuritis of beriberi and chronic alcoholism.

In the Nutrition Clinic at the Hillman Hospital, Birmingham, Alabama, there are under observation 700 pellagrins. In these cases it has become increasingly evident that the inadequate and unbalanced diet eaten by these patients predispose them simultaneously to a number of nutritional disorders. Thus we have found that pellagrins almost without exception suffer from an associated beriberi at some time during the course of their disease. The neuritis from which the ambulatory pellagrin suffers is not severe and it is usually limited to the lower extremities.

Spies and Aring (1938) studied the peripheral neuritis of pellagra and demonstrated that it could be relieved with thiamin, while other symptoms of pellagra remained stationary or progressed. These observations have been repeated on numerous occasions. The pain and numbness associated with the peripheral neuritis can always be relieved by the use of crystalline vitamin B1. The patients attending the nutrition clinic subsist on the same diet as they had been taking before coming under observation. Despite this fact, the symptoms of neuritis in the ambulatory pellagrin subside rapidly following the injection of 50 mg. of vitamin B1 on two successive days.

PERNICIOUS ANÆMIA.—About 75 per cent. of all cases of Addisonian pernicious anæmia have involvement of the nervous system, and in at least 25 per cent. of all cases neural or mental symptoms are the first indications of the disease. The symptoms arising from involvement of the nervous system are usually characterized by disorders of sensation, especially tingling of the hands and feet. About 10 per cent. of all patients having symptoms arising from the nervous system have degeneration of the posterior and lateral columns of the spinal cord. The peripheral neuritis in patients with pernicious anæmia cannot be distinguished pathologically (Greenfield and Carmichael, 1935) from the peripheral neuritis associated with pellagra, chronic alcoholism, and other conditions described above. It has been shown that the progression of the spinal cord and peripheral nerve lesions in pernicious anæmia can be averted by adequate amounts of a crude liver extract administered intramuscularly. Liver extracts administered a few years ago were considerably less refined than some that are now being dispensed and it may be that the more refined concentrates now in use will not protect against neural involvement. This point should be determined within the next few years. In general, it is believed that the more crude the liver extract, the greater is the content of vitamin B1.

Schiro, Spies, and Aring (1939) studied three cases of pernicious anæmia with signs of spinal cord degeneration and peripheral neuritis. With the administration of large amounts of brewer's yeast by mouth a reticulocyte response was obtained in these cases, and the red blood cells increased in number. Meanwhile the neurological signs progressed relentlessly and became so severe that the study had to be terminated. This was done by the use of large doses of liver extract, which halted the progress of the neurological signs. Before terminating the study in two cases, thiamin was given intravenously in 50-mg. doses twice per day for 10 days as a supplement to the yeast. This therapy had no effect on the progression of neurological signs over this short period. The peripheral neuritis in these cases of pernicious anæmia was complicated by the spinal cord lesions, which made evaluation difficult and limited the period over which therapy other than liver extract could be tried with safety.

At the present time the physician will do well to use the crude liver extracts, which have been proved to be effective in the treatment of spinal cord lesions associated with pernicious anæmia. Vitamin B1 preparations are, of course, theoretically valuable accessories and their use should not be denied.

DIABETES.—Attempts to explain the high incidence of neurological lesions in diabetes began with the original concept, suggested by Bernard's work, that the nervous lesions were the cause rather than the result of disturbed sugar metabolism. By the end of the first decade of the insulin era, arterio-sclerosis and vitamin deficiency were believed by most writers to rank high among the ætiological agents responsible for the neurological lesions.

Since the polyneuritis of diabetes and of beriberi may give rise to similar or identical symptoms, it was natural that crystalline vitamin B1 should be given to patients with diabetic neuritis. Published reports to date are surprisingly few, and though suggestive they are far from conclusive. Vorhaus, Williams, and Waterman (1935) included diabetic neuritis in a group of metabolic neuritides which improved following crystalline vitamin B1 therapy. Sciclounoff and Broccard (1936) described excellent results in five out of six cases of diabetic neuritis treated with preparations of crystalline vitamin B1 administered parenterally. Their case reports said little about concurrent diabetic control. One can feel confident that vitamin B1 deficiency does occur in certain diabetics, but what percentage of the cases of diabetic neuritis have vitamin B1 deficiency cannot be estimated with any degree of assurance. Nor can we state whether or not local ischæmia resulting from sclerosis of the arteries might predispose to some of the manifestations.

At the present time it seems that the prophylaxis against neuritis in diabetic patients, in addition to painstaking control of the diabetes, requires the prescription of diets adequate in the antineuritic vitamin. Sindoni (1936) has shown that several typical diets for diabetic patients are actually deficient in this vitamin. The diets used in the clinical management of diabetics in many hospitals are on the borderline of normal requirements and would be inadequate in the event of any additional requirement.

Since diabetes and vitamin B1 deficiency are common, the two will some-

times occur by coincidence in the same person. At the present time information is inadequate to state that the majority of cases of diabetic neuritis are caused by an inadequate amount of vitamin B1. The following theoretical considerations, however, favour the hypothesis that vitamin B1 deficiency may play a part in the ætiology of these changes : (1) the close relationship between vitamin B1 and carbohydrate metabolism ; (2) the similarity of the clinical and neuropathological pictures between diabetic neuritis and the neuritis associated with other diseases which are thought to be due to a lack of vitamin B1 ; (3) the realization that many diabetics subsist on diets which are low in vitamins.

TUBERCULOSIS.—Some investigators have suggested that the neuritis accompanying tuberculosis is associated with the accompanying emaciation. It is not uncommon to find neuritis associated with late tuberculosis, especially in institutions. We observed that the clinical manifestations of neuritis in three persons with tuberculosis were identical with those of the peripheral neuritis associated with the other diseases described here. The neuritis in these three patients developed while they were in the hospital and gradually disappeared following the administration of large amounts of yeast and a well-balanced diet.

PORPHYRINURIA.—It has been observed for some time that increased quantities of porphyrin may be excreted in the urine in febrile conditions, liver diseases, anæmia, and in poisoning by sulphonal, veronal, trional, lysol, chloroform, salvarsan, zinc, acetanilid, tin, and lead. Some writers regard this finding as a simple increase in the amount of normal porphyrin excretion resulting from the underlying disturbances in metabolism. In recent years it has been shown (Beckh, Ellinger, Spies, 1937) that a number of the metabolic and deficiency diseases which are accompanied by peripheral neuritis also are associated with the porphyrinuria and other abnormal urinary pigments. It seems likely that porphyrinuria occurs as a physiological process and that the amount excreted may be increased in certain diseases and intoxications. Very rarely porphyrinuria may be the chief symptom of a characteristic clinical syndrome of unknown ætiology. When this disease affects the nervous system, the first symptom is severe and constant pain in the extremities. This is usually accompanied by muscular weakness or flaccid paralysis. Pathological examination shows widespread degeneration of the myelin sheaths in the peripheral nerves and spinal cord. At present there is little information as to whether vitamin B1 bears a relationship to any of the neuritides associated with porphyrinuria or with the other abnormal pigments which are ether-soluble and give red colour in 25 per cent HCl. These urinary pigments do seem to accompany malnutrition.

SPORADIC CASES OF BERIBERI IN ASSOCIATION WITH MALNUTRITION.—Sporadic cases of beriberi are reported in the literature from time to time. However, isolated cases are often not recognized as true beriberi. Kepler (1925) reported a case in a negress who restricted herself to a diet of raw starch. At the end of three years she developed polyneuritis with œdema and an enlarged heart. We have observed the development of beriberi in 15 cases who restricted their diet to carbohydrates and fats. Following treatment with large

amounts of yeast, the symptoms disappeared. Urmy, Ragle, Allen, and Jones (1934) demonstrated that beriberi may follow a short-circuit operation on the small intestine and may be cured by disconnecting the intestinal anastomosis. Their cases show that beriberi may result from a lack of proper absorption. Many persons suffering from malnutrition have signs and symptoms clinically indistinguishable from those of beriberi.

Since most physicians rarely consider beriberi in differential diagnoses, we contend that the disease occurs much more commonly than is generally thought and, in fact, that it is endemic rather than sporadic.

The diagnosis of beriberi may be made if the patient has evidence of peripheral neuritis, with or without œdema, cardiovascular or gastrointestinal abnormalities, and a history of a diet deficient in vitamin B1. The laboratory is of little aid in the diagnosis of thiamin deficiency, as there is as yet no simple chemical test for the vitamin.

Williams and Spies (1938) have described in review the important work which led to the concept that certain types of neuritis are due to nutritional deficiency. The identification and synthesis of vitamin B1 by Williams and his associates (1934, 1936) made available large quantities of crystalline vitamin B1 and led to rapid progress in clinical research on this subject.

We have had experience with the neuritis of pellagra, pernicious anæmia, beriberi (" alcoholic and non-alcoholic neuritis "), tuberculosis, and pregnancy. These neuritides, excepting possibly the neuritis encountered in pernicious anæmia, respond promptly to large doses of vitamin B1. We usually administer thiamin intravenously, giving 50 mg. twice per day for 1 week. The initial response to this therapy is usually rapid. Pain is greatly relieved within 24 hours, and the strength, accuracy, and the speed of movement is usually improved within 3 days, this improvement possibly being due to the conspicuous relief of pain. If analgesics have been used, they may be discontinued at this time and patients who have slept little or not at all for weeks may be able to sleep with no medication, other than vitamin B1. The relief which usually occurs in this group of nutritional deficiency neuritides is abrupt and dramatic. Patients previously bedfast may be able to walk within a few weeks. However, the patient quickly reaches a stage beyond which thiamin will not cause further improvement, and residual changes may persist indefinitely.

Nothing more than the relief of pain and slight early improvement in motion may be expected from vitamin B1 therapy in the extremely severe case of neuritis in which there has occurred practically complete paralysis of all of the extremities. These patients run their natural course of recovery, which requires months and even years, with or without vitamin therapy.

It is our thought that the initial prompt improvement with thiamin in cases of nutritional deficiency may be humoral in nature. This impression is furthered by the work of Minz (1938), who has been able to show that vitamin B1 enhanced the effect of acetylcholine in the transmission of the nervous impulse. It seems that vitamin B1 inhibits cholinesterase in the same manner as does eserine. In our patients in which tests for cholinesterase were performed (*in*

vivo), the serum cholinesterase tended to be inhibited by the administration of thiamin. Glick and Antopol (1939) obtained similar results with horse and rat serum (*in vitro*), and they made the important observation that the inhibition of the serum cholinesterase was obtained only with concentrations of vitamin B1 in excess of those known to occur in the living organism.

We have studied the peripheral nerve histologically by the biopsy method in 12 cases of deficiency disease with neuritic symptoms, in several instances both before and months after treatment with crystalline vitamin B1. In all cases marked loss and degeneration of myelin sheaths was observed in the terminal portions of the internal branch of the anterior tibial nerve. The axones in these peripheral nerves have been, on the whole, normal. In those cases in which the peripheral nerve was examined as long as 11 months after treatment was instituted, the loss of myelin sheaths was severe.

This study lends support to the hypothesis that the initial spectacular improvement following vitamin B1 therapy, which is experienced by sufferers from nutritional neuritis, is on a humoral basis. It also illustrates how slowly restitution of the nerve may occur.

Use of Cocarboxylase

In 11 cases of moderate nutritional neuritis the administration of cocarboxylase * (phosphorylated thiamin), 10 mg. in sterile physiological solution of sodium chloride twice daily, by intravenous injection, resulted in the same improvement that had been seen following the use of thiamin. This result supports the hypothesis that vitamin B1 may be utilized as cocarboxylase by the body (Spies, 1939). Cocarboxylase is a fundamental oxidative-reductive enzyme in the body. Lewy, Himwich, Frostig and Spies (1939) have described that " the administration of 50 milligrammes of cocarboxylase (Merck) to persons who exhibited signs of an ' active process ' was followed, in every instance, by dramatic and rapid improvement. The bisulfite-binding substances decreased in quantity. The pathological signs of peripheral and cranial nerves, which had become increased in patients who were being treated with nicotinic acid and riboflavin, became less conspicuous or disappeared. The irritability of a number of muscles, measured in terms of their strength-duration curves, returned from underexcitability before treatment to normal values and in some cases even progressed to overexcitability. Correspondingly, the increased threshold of sensibility to touch and prick in arms and legs was reduced to normal, and the depressed pupillary and corneal reflexes improved quantitatively, often becoming normal.

Following the administration of cocarboxylase, some beneficial effect occurred, in some persons within an hour and in all persons within four hours. Improvement continued for from one to four days thereafter. Since the unbalanced diets of these persons remained essentially unchanged, in the absence of further therapy the patients tended to regress rapidly to their condition preceding treatment. A psychoneurotic syndrome which was recognized in these persons and which responded promptly to the administration of cocarboxylase

* Furnished through the courtesy of Merck and Company.

will be described separately. In contrast, in the persons selected for control, there was no decrease of bisulfite-binding substances in the book and no improvement in the neurological and psychoneurotic symptoms following cocarboxylase therapy."

Wernicke's Pseudo-encephalitis

Wernicke's pseudo-encephalitis has been produced by Alexander, Myerson, and Pijoan (1938) in the pigeon by the feeding of diets low in vitamin B1 and high in other vitamins (A, B, C, and D). They have not produced the disease by a diet low in vitamin B1 except in rare instances. The feeding of an excess of the other vitamins seems to be a requisite in the production of Wernicke's disease in their experience. Wernicke's disease is rarely encountered in man, and when its clinical incidence is reported in large numbers the diagnosis should be accepted with caution. The work of Alexander, Myerson, and Pijoan warrants a trial of thiamin in these cases, though these workers have not yet attempted to cure their pigeons with vitamin B1.

Use of Vitamin B1 in the Treatment of Pain and of Tabes Dorsalis

Vitamin B1 probably has been administered to patients suffering from almost every kind of nervous disease. Like other new forms of therapy (insulin, liver extract, sulfanilamide), it has been applied in the attempt to treat many diseases.

Our experience with patients suffering from severe pain (carcinoma, cord tumour, brachial and trigeminal neuralgia) was that thiamin, administered intravenously in 50–100 mg. daily over a period of 10 days, did not act as an analgesic. We have administered thiamin intravenously (100 mg. in normal physiological saline solution) during the crises of tabes dorsalis in six patients. This procedure was recommended by Metildi (1939). We have observed complete relief of the crises for varying periods after the injection. In every case with the return of pain, normal physiological saline solution was given intravenously. The saline solution alone was as efficacious in the relief of tabetic crises as was the thiamin dissolved in saline solution. We have, as yet, no explanation for this phenomenon.

We are unable to evaluate the recommendation in the literature that other neurological conditions may be improved with the use of vitamin B1, but it is our belief that vitamin B1 is useful in the amelioration of these disorders only if they are caused by a deficiency of vitamin B1. It is often difficult to make a clinical diagnosis of vitamin B1 deficiency with any degree of assurance, but this defect may be remedied shortly by the development of simple diagnostic laboratory methods.

Chemistry of Vitamin B1

Thiamin hydrochloride in its phosphorylated form (cocarboxylase) is an important enzyme which plays a prominent role in oxidation and reduction. There is much to suggest that thiamin may act other than as a pyrophosphate. It seems that so far as the formation of the pyrophosphate is concerned the

alcohol group of the thiazole side-chain is necessary. At the present time it is wise to suppose that thiamin is a unique or almost unique molecule which cannot undergo much alteration without impairment of physiological activity.

Prevention and Treatment of Vitamin B1 Deficiency

Vitamin B deficiency can be greatly decreased by the application of the following recommendations : (1) fresh foods such as potatoes, native vegetables, pork and liver, eggs, milk and fruits, and especially beans and whole grain cereals and dried or canned foods should be included in the diet whenever possible. (2) The use of dried yeast, wheat germ, liver, kidney, and vitamin B1 crystals as supplements to the diet should be encouraged whenever possible. The expense of such materials, however, often interferes with their extensive use. (3) Since vitamin B1 is water-soluble, a large amount of it is lost when the water in which the foods are cooked is thrown away. It is recommended, therefore, that the water in which foods containing vitamin B1 are cooked be used, for broths. Whole barley or other grains which are rich in vitamin B1 may be added to such broths to insure additional protection. (4) The use of undermilled rather than overmilled grains should be rigidly enforced among government troops and in prisons, asylums, and other institutions where mass feeding is required. Only about 6 per cent. of the vitamin B1 content remains in white flour. Each lot of grain purchased should be examined to determine whether there is an adequate amount of the germ and of the external layers of the grain. Since molds, weevils, and other infestations deprive cereals of this vitamin, one must be certain that the grain has not spoiled. (5) Particular attention should be directed toward the diets of persons with chronic debilitating diseases and increased metabolism, for the incidence of vitamin B1 deficiency is high among such people. Chronic alcoholic addiction, pellagra, sprue, pernicious anæmia, colitis, diabetes mellitus, tuberculosis, senility, malignancy, cirrhosis, and other diseases may interfere with the proper nutrition of the patient and thus predispose to the development of vitamin B1 and nicotinic acid deficiency. (6) The diets of pregnant and lactating women should be especially rich in vitamin B1. Whenever there is any doubt as to the adequacy or utlization of this vitamin either in the mother or in the child, supplements should be given. The supplements should be continued for the mother and child until the proper diet is assured. The nursing mother should receive at least 5 mg. of thiamin or its equivalent daily ; the infant should receive 0·5 mg. of thiamin or its equivalent, and children should receive 1 mg. or its equivalent per day. (7) The requirement for vitamin B1 may be distinctly above the average in persons with fever, severe gastro-intestinal symptoms, hyperthyroidism, and other conditions. It is essential for the physician to prescribe amounts above the average for such persons. The authors suggest for such a maintenance dose, from 5 to 10 mg. of pure vitamin B1 or its equivalent, except when the patient is unable to absorb from the gastro-intestinal tract. In such instances it is essential that vitamin B1 be given parenterally in order to protect the person from a deficiency of this vitamin.

Clinical Indications for Vitamin B1 Therapy

The Council of Pharmacy of the American Medical Association (1936) has recently stated that it considers the following to be allowable claims for the use of vitamin B1 in therapy : (1) May be cited as of value in correcting and preventing absence or loss of appetite—anorexia—of dietary origin in certain cases. (2) Of value in securing optimal growth of infants and children. (3) Of value in correcting and preventing beriberi. (4) Because it is a dietary essential and its administration in concentrated form is of value in some conditions where difficulty in utilizing ordinary foods in the usual way is encountered. (5) There are many experimental indications in the literature indicating other possible functions of vitamin B1, e.g. an influence on intestinal motility and neuritis of various types and also indications of greatly augmented requirement when metabolism has increased as in hyperthyroidism, neuritis of various types, and infection. It seems too early to permit advertising claims for these items.

The authors support these claims and the method in which they are presented. However, we feel that since the time of their publication in 1936, additional information has become available which indicates that persons having polyneuritis associated with chronic alcoholism, pellagra, or pregnancy are greatly benefited by the administration of this material. There is enough clinical information available at the present time to warrant the trial of thiamin in patients who have peripheral neuritis secondary to dietary deficiency or associated with under-nutrition from any cause. Also a trial is warranted in peripheral neuritis and œdema of undetermined origin, though it is obviously too early to permit advertising claims for this latter group.

It is probable that in the near future, simple diagnostic clinical and laboratory methods for the determination of vitamin B1 deficiency will become available. Using a fluorescence method, Cline and his associates (1938) devised a method for determining excretion of vitamin B1 in the urine.

Specific Treatment

The essence of treatment lies in the administration of adequate amounts of foods rich in vitamin B1, supplemented if possible with large amounts of a specific therapeutic agent. The foods included in the dietary will depend upon the age, race, habits, tastes, and financial status of the patient concerned.

For an adult a well-rounded diet of 4,500 calories, including fresh native vegetables and fruits, whole-grain cereals, peas, beans, barley, pork and liver, eggs, milk, and other foods of high vitamin B1 value should be the objective. Whenever possible this diet should be supplemented with one or several of the following curative therapeutic substances, for even in chronic resistant cases which are cured slowly these substances are of benefit in relieving symptoms and in shortening convalescence : dried brewers' yeast (6 ounces daily) ; wheat germ (6 ounces daily) ; extract of rice polishings (tikitiki) (3 ounces daily) ; or crystalline vitamin B1 (10 mg. twice daily). In cases of severe beriberi even larger doses of crystalline vitamin B1 may be indicated. In such cases it seems wise to administer 20 mg. until the signs of avitaminosis have disappeared. In cases of mild deficiency doses of 5 mg. daily are adequate.

Our experience leads us to believe that if crystalline vitamin B1 is to be effective in any very serious nervous disease it must be given in large doses. We recommend the administration of at least 50 to 100 mg. each day, given parenterally in several doses of 10 to 20 mg. each. It is our belief that if no response is obtained within a week, further vitamin therapy will be unavailing. There is practically no danger of overdosage with thiamin. We have administered 500 mg. intravenously daily for 1 month, and have given 500 mg. daily by mouth over a period of 3 months.

At present there does not appear to be any reason to administer thiamin intraspinally. In our experience thiamin is rapidly transmitted from the blood into the cerebrospinal fluid, where it may be found in increasing amounts 1 hour after intravenous injection.

The clinical response to vitamin B1 therapy is often dramatic. In the acute cases beginning improvement may be noticed within a few hours ; the mild cases are often relieved within 24 to 48 hours. In the chronic case there is often great relief, particularly from pain, within a few days, though other signs may remain for a long period. Occasionally, in chronic cases, some residual changes remain indefinitely. It is generally recognized that the maintenance requirement and the curative dose of vitamin B1 vary from one individual to another and may vary in the same individual from time to time. These variabilities necessitate close medical supervision at all times.

Nicotinic Acid Deficiency

Pellagra

Mental changes as a part of the pellagra syndrome have been recognized by many physicians, and in areas where the disease is endemic these symptoms are so common and so striking that they have become associated with pellagra even by the lay observer. Various abnormal psychic states have been described in medical literature on pellagra, and some writers have thought that one or another psychosis was typical of this disease. Subclinical pellagrins are noted for the multiplicity of their complaints, among which are many that are usually classified as neurasthenic. Practically every patient who finally had lesions characteristic of pellagra had been diagnosed previously as neurasthenia. The conduct of the pellagrin may be normal ; but he feels incapable of mental or physical effort, even though he may be ambulatory.

The noticeable and more serious mental signs of pellagra manifest themselves in various types of psychoses. The most common is perhaps that in which loss of memory, disorientation, confusion, and confabulation are predominant. There are also types in which excitement, mania, depression, and delirium may occur. In our experience a paranoid condition is common in pellagrins. These patients, acting on their paranoid delusions, are more active than are other pellagrins with psychoses.

Elvehjem, Madden, Strong, and Woolley (1937) reported that nicotinic acid cured blacktongue in dogs, a canine disease which is believed to be analogous to pellagra in human beings. Since all food substances which have been found

to be curative and preventive for canine blacktongue have likewise proved beneficial in the treatment and prevention of human pellagra, investigators were encouraged to determine the effect of nicotinic acid on this disease. Spies, Cooper, and Blankenhorn (1938) showed that pellagrins responded dramatically to the administration of this drug. Beneficial results had also been observed independently by other investigators in the field. Spies, Sasaki, and Gross (1938) and Spies, Bean, and Stone (1938) mentioned briefly that the early and late mental symptoms of pellagrins in relapse and of sub-clinical pellagrins were relieved by nicotinic acid. In a larger series of cases it was possible to institute control measures in order to study more specifically the mental symptoms of pellagrins in relapse and their response to nicotinic acid. Related studies on subclinical and mild cases have also been made.

Acute Psychoses

We have been able to relieve quickly the acute psychoses of 70 pellagrins with the use of nicotinic acid (Spies, Aring, Gelperin, Bean, 1938). The psychosis had been present from 1 to 83 days in these cases, and in 10 of these patients the psychosis had been induced in the hospital. Five hundred to 1000 mg. of nicotinic acid was administered daily to these patients, in 50 mg. doses.

The relief of the numerous and varied abnormal mental signs in this group of pellagrins was dramatic in its suddenness, and was maintained as long as nicotinic acid or a well-balanced diet supplemented with nicotinic acid was administered. There was no instance in these 70 psychotic pellagrins in which we were unable to relieve the psychosis. Further experience has upheld the efficacy of nicotinic acid in the treatment of this type of patient. The amide of nicotinic acid (sodium nicotinate) acts similarly to nicotinic acid in these cases.

Chronic Psychoses

We were unable to relieve completely the chronic psychoses accompanying pellagra in 13 cases. Large doses (500 to 1000 mg. daily) of nicotinic acid were administered for periods varying from $1\frac{1}{2}$ to $2\frac{1}{2}$ months to these pellagrins suffering from chronic psychoses. These patients became more alert, cooperative, and tidy, and apathy and restlessness disappeared. Most of these patients changed from bedridden to ambulatory patients. Similar beneficial results have been obtained recently following the administration of similar doses of either the monocarboxylic acid of pyrazine, or quinalinilic acid.

Several reports (Evans, 1939 ; Bogart, 1938 ; Frontali and Ferrari, 1938) have appeared on the beneficial effect of nicotinic acid in the psychoses of pellagra. There has been no report of the complete relief of a chronic pellagrous psychosis of many years' duration. In only two cases, who had been in mental hospitals for 9 and 8 months respectively, were we able to effect anything approaching complete cure of the chronic psychoses of pellagra. These cases are too few on which to base a final opinion.

"Neurasthenia"

Nicotinic acid was also administered to a group of 225 mild pellagrins, with complete relief of their rather typical complaints, which have usually been considered to be those of neurasthenia (Spies, Aring, Gelperin, and Bean, 1938). The more common symptoms in this multiplicity of complaints are fatigue, insomnia, anorexia, vertigo, burning sensations in various parts of the body, numbness, palpitation, nervousness, a feeling of unrest and anxiety, headache, forgetfulness, apprehension, and distractibility. On nicotinic acid therapy, the ambulatory pellagrin also regains energy and appetite. This relief occurs within 1–12 days following the administration of from three to six doses, 100 mg. each, of nicotinic acid per day.

Stupor

It should be emphasized that many people develop the mental signs of pellagra, at least to a mild degree, long before they develop other manifestations of the disease. We have treated with nicotinic acid 60 cases, who had mental symptoms ranging from psychoses to stupor, without any clinical evidence of pellagra other than malnutrition and a positive test for porphyrins or related substances in the urine. This test (Beckh, Ellinger, and Spies, 1937) is suggestive of a nutritional deficiency, but not diagnostic of pellagra. These patients were promptly relieved by nicotinic acid. Eleven other cases with stupor or psychoses with a negative urinalysis responded to nicotinic acid. Our experience and that of Sydenstricker, Schmidt, Fulton, New, and Geeslin (1938) suggests that it is advisable to use nicotinic acid as a therapeutic test in such individuals. Five hundred to 1000 mg. given in 10 equal doses during each 24 hours for a period of 2 weeks is inexpensive and may result in a miraculous cure.

Deafness

Selfridge (1939) reported improvement in the hearing of patients with high-tone deafness with the use of nicotinic acid. We have observed that pellagrins are better able to hear after the administration of large amounts of nicotinic acid, probably due to an improvement in their mental state and a diminution in their tinnitus and dizziness.

Chemistry of Nicotinic Acid

Nicotinic acid, as well as thiamin hydrochloride and riboflavin, are components of important intracellular enzymes.

Nicotinic acid in its amide form is an important constituent of cozymase (von Euler, Hebers, and Schlenck, 1935) and of coferment (Warburg and Christian, 1936). It has been shown (Vilter, Vilter, and Spies, 1939) that in severe pellagra in relapse the blood level of codehydrogenases I and II (cozymase and coferment) is below normal and that these coenzymes may be returned to their normal levels in the blood by the administration of nicotinic acid or its amide. It would seem that persons with pellagra have less of these fundamental enzymes in their tissues than do normal persons. Evidently nicotinic

acid is changed into nicotinic acid amide, and nicotinic acid amide is built into the molecule of cozymase and coferment. This might account for the delay which occurs between the administration of nicotinic acid and the elevation of these substances in the blood.

Prevention and Treatment of Nicotinic Acid Deficiency

The dietary advice noted under the prevention and treatment of thiamin deficiency is as applicable to the pellagrin as to those suffering from vitamin B1 deficiency.

The optimum dosage of nicotinic acid, like that of thiamin, has not been determined. Neither has the minimal dose of nicotinic acid been determined but it seems to vary from case to case. It is thought that patients with severe mental symptoms should receive a total of at least 500 mg. per day. This is best administered by mouth in 10 equal doses, although it may be administered parenterally. In the extremely severe cases convalescence may be shortened by the administration of 1,000 mg. daily. We have administered as much as 2,000 mg. daily in divided doses without untoward results. There may be some flushing and feeling of warmth in the skin incident to large doses of nicotinic acid.

The dosage of nicotinic acid amide and sodium nicotinate is similar to that of nicotinic acid.

Nicotinic acid may be administered intravenously in dilute solutions. The nicotinic acid should be dissolved in sterile physiological solution of sodium chloride. Nicotinic acid may be given intramuscularly with slight discomfort. A solution containing 5 mg. of nicotinic acid per c.c. of normal saline should be used. These solutions may be sterilized by boiling or autoclaving, as nicotinic acid is heat stable. The total daily dose of nicotinic acid when given parenterally varies from 40 to 80 mg. This total dosage should be given in divided doses of 10–15 mg. each.

Riboflavin (Vitamin B2) Deficiency

The use of riboflavin in the human (Sebrell and Butler, 1938 ; Vilter, Vilter, and Spies, 1939) has been in conditions other than those associated with neurological disease. We have seen peripheral neuritis become worse in persons with the healing lesions of riboflavin deficiency (roughening of the skin around the mouth and across the tip of the nose) during the administration of riboflavin. The amounts of riboflavin given to cure these lesions do not affect the peripheral neuritis ; also peripheral neuritis develops in persons getting large amounts of riboflavin but eating a diet deficient in vitamin B.

Vitamin B6 Deficiency

This substance, recently synthesized in small amounts, has been used in a study (Spies, Bean, and Ashe, 1939) of four cases of nutritional deficiency. In instances of multiple deficiency the addition of thiamin chloride, nicotinic acid, and riboflavin to the inadequate diet produced great relief from beriberi,

pellagra, and riboflavin deficiency. If the diet is unchanged symptoms may remain or develop which are not corrected by these substances. The most obvious symptoms are irritability, insomnia, nervousness, vomiting, weakness and difficulty in walking. The gait may resemble that seen in acute cerebellar disorders ; it is wide-based and reeling. Cachexia may supervene.

Spies, Bean, and Ashe (1939) administered 50 mg. of synthetic vitamin B6 in sterile physiologic solution of sodium chloride intravenously to four of these patients, with abrupt improvement in all of them. Within 24 hours the symptoms, with the exception of the cachexia, disappeared. One of these individuals who could stagger only a few steps walked two miles within 24 hours after the injection of 50 mg. of vitamin B6. All patients noted conspicuous gain of strength and a feeling of well-being after a single injection.

Observations are being made on the possible relationship of this substance to the nervous diseases due to nutritional deficiency.

Multiple Vitamin Deficiency

We have discussed the deficiencies of portions of the vitamin B complex and the nervous manifestations therefrom in terms of distinct entities. As one's experience with these diseases increases the realization becomes stronger that the majority of patients suffering from nutritional deficiency are affected by a lack of more than one substance. This point of view has already been suggested by the clinical work that has proceeded with vitamin B6 and which has been described in a preceding paragraph.

In the Nutrition Clinic at the Hillman Hospital in Birmingham, Alabama, close watch has been kept on the pellagrins for symptoms of beriberi and riboflavin deficiency. It has been found that practically all pellagrins have, or have had, symptoms of peripheral neuritis. If these symptoms are absent, abnormality of the nerves can be demonstrated in active pellagrins with a chronaximeter (Lewy, Aring, and Spies, 1939). The neuritis in ambulatory pellagrins is, as a rule, not severe and is usually limited to the lower extremities. It can be made to regress and reappear, depending upon the administration or the witholding of thiamin chloride.

Symptoms of riboflavin deficiency in pellagrins, while not as common as those of beriberi, occur often enough to warrant its inclusion in the conception of multiple deficiency.

It is to be expected that nutritional disorders should be associated one with the other. In foodstuffs the water-soluble vitamins are often associated, and a diet deficient in one substance is almost certain to be deficient in others. Inadequate and unbalanced diets eaten by the majority of patients predispose them simultaneously to a number of nutritional disorders, and the diagnosis of one clinical deficiency syndrome necessitates a thorough search for others.

The multiple nutritional deficiencies have been studied (Spies, Vilter and Ashe, 1939) chiefly by administering a pure vitamin and observing the relief of certain of the symptoms, diagnostic of the syndrome for which the agent is specific, but no improvement of the lesions of associated syndromes, so long as the diet of the patient remains constant.

Pathology of Avitaminosis

This portion of the subject has been covered recently by Greenfield (1938) in this journal.

In our studies of the biopsies of peripheral nerve in 12 cases of deficiency disease with neuritic symptoms, in several instances both before and months after treatment, there have occurred loss and degeneration of myelin sheaths in the terminal portions of the anterior tibial nerve. We have not seen this degeneration in its active phase, but only after the destruction and removal of the products of degeneration had occurred. The axones in these peripheral nerves on the whole have been normal. In those cases in which the peripheral nerve was examined as long as 11 months after treatment was instituted, the myelin sheath loss was as severe as it was before treatment was begun. This relationship of vitamin B1 deficiency to degeneration of the peripheral nerves is well known. Bertrand, Liber, and Randoin (1934) found that the katabolism of myelin in a degenerating nerve ceased in pigeons deficient in vitamin B1. Associated with this phenomenon was inactivity of the sheath cells of Schwann. After treatment with vitamin B1 the Schwann cells became active and phagocytosis of the degeneration products of myelin occurred. Vitamin B1 appears to be a requisite in the repair of the nerve fibre.

In recent years, however, there has been a strong tendency to consider many of the pathological changes of experimental beriberi the result of starvation rather than the result of a vitamin B1 deficiency. Particularly significant in support of this idea is the general opinion among investigators that one of the earliest results of a deprivation of vitamin B1 is failure of appetite. Chamberlain, Bloombergh, and Kilbourne (1911) demonstrated that fowls dying from starvation had degeneration of the peripheral nerves which could not be distinguished readily from the degeneration found in polyneuritis gallinarum induced by an exclusive rice diet. Davison and Stone (1937) believe that the pathological changes in the nervous system in animals suffering from inanition are essentially the same as those in animals deprived of vitamin B1 or B2. Vedder and Chinn (1938) compared the brachial and sciatic nerves of rats subjected to complete starvation, rats completely starved but given 3 mg. of crystalline vitamin B1 orally each day, and rats given a diet deficient in vitamin B1. Myelin degeneration was seen in the peripheral nerves of all rats of all groups. No appreciable difference in the extent of this degeneration was noted in the three groups. Sebrell and Elvove (1931) have shown that an inadequate amount of vitamin B1 added to the vitamin B1 free diet of rats makes the neuritis more severe than if no vitamin B1 is added. It is essential that further studies on the physiological action of vitamin B1 be made before we can determine how definite a role inanition plays in the development of polyneuritis in vitamin B1 deficient animals.

Human beings, however, often develop the lesions while maintaining normal body weight. From studies on human beings it is thought by the authors that diets deficient in other essential factors increase the requirement for vitamin B1 and that this substance is not stored in the body to the extent that we previously

thought. It would seem, therefore, that these factors play a significant role in the development of clinical beriberi in human beings.

Experimental polyneuritis in fowls usually is in many ways comparable to dry beriberi in man. In the experimental animal, as in the human being with vitamin B1 deficiency, the greatest degeneration is in the peripheral nerves, especially the distal portions, the sciatic nerves being particularly affected. Vedder and Clark (1912) showed that in experimental neuritis practically every fibre of the nerve has some evidence of degeneration, though the extent varies greatly in the fibres of the same nerve. The myelin is degenerated and there is swelling of the nerve-sheath in 10 to 15 per cent. of the fibres. Vedder and Clark described the earliest stage of myelin degeneration as slight swelling of the medullary sheath and a tendency toward segmentation at the circumference. There are generalized changes affecting the peripheral nerves, the ventral and dorsal nerve roots, all tracts of the spinal cord, the medulla, pons, midbrain, and internal capsule. There is also degeneration of the nerve cells. These changes in the nervous system appear similar to those described in human beriberi. It is thought, however, that in order to produce lesions similar to or identical with those appearing in human beings some vitamin B1 must be fed to the experimental animal in order to prevent early death.

The nervous lesions of pellagra are not as definite as those associated with lack of vitamin B1. Goldberger, Wheeler, Lillie, and Rogers (1928) produced in dogs a condition associated with black tongue which they thought resembled human pellagra, but they did not reproduce the nervous lesions of the human disease. Only slight degeneration was found in the peripheral nerves and dorsal columns in those dogs that survived longest. Stern and Findlay (1929) produced in rats a similar condition associated with lesions of the epidermis and some degree of paralysis, but without definite changes in the peripheral nerves or tract lesions in the spinal cord. Zimmermann (1937) used a diet from which he believed vitamin B2 was excluded. In the more chronic disease which he produced the degeneration was very marked, both in the peripheral nerves and dorsal columns. The similarity of these changes to those seen in cases of pellagra is evidence of the relation of this disease to lack of vitamin B2, although there are differences between the human and the experimental disease. Zimmermann stated that the anterior horn cells and Betz cells in his dogs were normal, whereas in the human disease the latter cells suffer, along with many other cortical neurones, from the chromolytic changes which Adolf Meyer (1901) called "central neuritis." On the other hand, Stern and Findlay found changes in the neurones, but none in the tracts of the cord or peripheral nerves in rats deprived of vitamin B2. Bessey, Boyle, and Wolbach (1937) have confirmed this work with rats. Obviously rats respond differently.

In the human disease the long tracts of the cord may or may not be affected. This is possibly a factor which influences the severity and duration of the pellagra. Usually the dorsal columns are more affected than the anterio-lateral columns, but in a case reported by Langworthy (1931) the reverse was the case. In Greenfield's (1938) cases the degeneration appeared to differ from that of subacute combined degeneration in that there was very little evidence of

vacuolation in the early stages. It seemed to be a true Wallerian degeneration, and in the dorsal columns was related to degeneration of the entering spinal roots. In some of Pentschew's (1929) cases in which the duration of the illness was longer, asymmetrical areas of sclerosis were found on the margins of the antero-lateral columns.

Persistent Problems

If it has not been indicated already, many of the concepts are unsettled in the field of nutritional deficiency. The number of problems that remain to be solved furnishes an index of our comparative ignorance of the vitamin deficiencies that affect the nervous system. The more pressing problems awaiting the worker in this field will be described briefly.

The relationship to nervous disease, of deficiency of vitamins besides those of the B complex that have been synthesized, has not been explored in man. This is no doubt due to the inability to obtain sufficient quantities of the pure vitamin. The work of Mellanby (1934) with vitamin A and of Einarson and Ringsted (1938) with vitamin E in animals is provocative.

The definite relief of pain (neuralgias, tabes), in certain instances, with the use of vitamin B1 needs elucidation. Vitamin B1 does not appear to be an analgesic (except in patients with nutritional neuritis). Neuralgia and tabes dorsalis do not appear to be vitamin deficiencies. In the experience of many workers the neuralgias are not benefited by the use of vitamin B1. It is possible that the concept of nutritional deficiency may have to be expanded in some instances to include many diseases now thought to be outside of its scope.

Why is it wellnigh impossible to produce neuritis in a normal man not previously deficient in vitamins by the use of diets nearly totally deficient in vitamin B1 ? It is well known that vitamin B1 is not stored to any extent by the body.

In consideration of the frequency with which acute psychotic episodes occur in pellagra, why are the chronic psychoses so rare in pellagrins who have had the disease for years ? The paucity of cases of psychoses due to pellagra in the custodial mental hospitals in the State of Alabama is striking.

There is disagreement about the neuropathology of the vitamin deficiencies in man. Possibly the conception that the great majority of the nutritional deficiencies are deficiencies of many vitamins may aid in the interpretation of the varying pathological findings. A report of the neuropathological lesions found in the cases that we have studied will be published at a later date.

Summary

Vitamin B1 is more appropriately termed the " anti-neuritic vitamin " than would be any other single nutritional element. Careful and controlled work has demonstrated the necessity for vitamin B1 in the repair of nerves damaged by a lack of this vitamin in the diet. The rapid relief of the discomfort of neuritis and therefore improved motor function in man suffering from nutritional

neuritis is a common observation. This improvement is most likely humoral in nature. Identical histological changes have been demonstrated in man in peripheral nerve twigs before and at varying intervals after symptomatic response to treatment.

It is unlikely that lack of vitamin B1 is the sole cause of nutritional neuritis in man, as one can reach a certain stage with thiamin therapy, beyond which improvement does not progress with continued vitamin B1 administration. This same type of improvement may be obtained in cases of neuritis now thought to be due to causes other than nutritional deficiency (brachial neuritis, emetine neuritis).

Our experience leads us to believe that if vitamin B1 is to be effective in any very serious nervous disease it must be given in large doses. We recommend the administration of at least 50–100 mg. each day, given parenterally in several doses of 10–20 mg. each. It is also our belief that if no response is obtained within a week, further vitamin B1 therapy will be unavailing.

Nicotinic acid has been proved to be a potent substance in the relief of the somatic complaints and of the acute psychoses associated with pellagra. Cases with chronic psychoses and pellagra are almost invariably benefited by this portion of the B complex and, in rare instances, are cured.

It has been suggested that thiamin and nicotinic acid which are perhaps essential to all cell life act through fundamental oxidative-reductive mechanisms of the body, the former through cocarboxylase, the latter through coenzyme or coferment. Since normal intracellular metabolism depends in large part upon the close interrelation of many enzymes, we may postulate that the pathological physiology of the deficiency states will be better understood when we have final information as to the nature and function of these enzymes.

Perhaps nowhere in the field of medicine is such prompt and lasting relief of symptoms obtained as that which follows administration of adequate amounts of these materials. While they cut down the time required for convalescence it must always be kept in mind that the administration of the vitamins does not replace the well-balanced diet.

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*Insuffisance Pituitaire et Schizophrénie. Considérations Anatomo-Cliniques sur l'Existence d'un Facteur d'Insuffisance Pituitaire dans Certains Cas de Schizophrénie. (Anatomoclinical considerations on the existence of a factor of pituitary insufficiency in certain types of schizophrenia.) M. Cahane and T. Cahane. 214.

*L'Insulinotherapie par Voie Endo-Veineuse. (Insulin therapy by intravenous injection.) Bardenat and Leonardon. 220.

Pituitary Insufficiency in Schizophrenia.—A case is described of a schizophrenic woman of about 33 years old who showed an abortive form of Simmond's disease. The patient died from influenza. Autopsy revealed changes in the pituitary, thyroid, ovaries, and suprarenals indicative of hypofunction.

Intravenous Insulin Therapy.—Using intravenous injections of insulin it was found that the phase antecedent to coma was diminished very considerably and that the phase of mental excitation was suppressed.

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*Sur Quatre Cas de Psychose Hallucinatoire. Essai d'Interprétation. (Four cases of hallucinatory psychosis. An attempt at interpretation.) P. Cossa. 357.
*Un Cas d'Hallucinose Auditivo-Visio-Cénesthésique en Relation Possible avec une Otopathie Ancienne. (Auditory-visual-kinæsthetic hallucinosis, possibly related to an old-standing ear trouble.) E. Escat and M. Escat. 381.
*Manie et Inspiration Musicale. Le Cas Hugo Wolf. (Mania and musical inspiration. The case of Hugo Wolf.) R. Pauly and H. Hecaen. 389.
Résultats du Traitement de 50 Cas de Paralysie Générale par la Malaria et le Stovarsol Sodique. (Results of treatment of 50 cases of G.P.I. by malaria and stovarsol.) M. Feuillade. 406.

Hallucinatory Psychosis.—Four cases of hallucinatory psychosis are described, each of which suffered from some somatic disease. One case had syphilis, two hyperthyroidism, and the fourth a severe gastro-intestinal infection. The author attempts to assess the extent to which the psychoses is in a causal relation to the somatic disturbance.

Auditory-Visual-Kinaesthetic Hallucinosis.—The question discussed at some length is the part played by the peripheral sensory disturbance in the genesis of the hallucination.

Mania and Musical Inspiration.—The life-history of this talented musician reveals an alternation of states of creative activity with states of artistic impotence. It would appear that during the creative periods, Wolf was in a hypomanic condition.

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*Zum Verhalten des Gehirns nach Injektion von Goldsalzen. (The brain after injection of gold salts.) W. J. Roberts. 744.
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Untersuchungen zur Pathogenese der luischen und tonischen Pupillenstörungen. (Investigations into the pathogenesis of luic and tonic pupillar abnormalities.) E. H. Romberg. 785.
Über den Nachweis von Gehirnmissbildungen durch das Röntgenbild und über seine klinische Bedeutung. (Diagnosis of developmental abnormalities of the brain by X-ray examination.) A. Bannwarth. 805.

Ocular Symptoms with Cardiazol and Insulin.—The author finds during cardiazol convulsion, and sometimes preceding it, spasm of the retinal arteries and dilatation of the veins. Sometimes the edges of the discs get blurred. During insulin shock dilatation of the retinal veins without arterial spasm was found regularly. The intra-ocular pressure was high in 13 out of 20 patients. This increase was even present on rest days, but disappeared when the treatment was stopped. (S. L. L.)

Distribution of Gold in Brain.—Experiments on the regional distribution in the brain of injected gold salts (Sanocrysin). The greatest amount is deposited in the nerve cells of nuclei oculomotorius, hypoglossus, dorsal vagi, in Purkinje cells, anterior horn cells, and the infundibulum. Among glia cells the oligodendroglia is the least active. The choroid plexus contains considerable quantities. Details about the histochemical method and the results should be read in the original. (A. M.)

Vol. 110. No. 1. June 1939.

*Die encephalen Tumoren des verlängerten Markes, der Brücke und des Mittelhirns. (Tumours of medulla, pons, and midbrain.) O. Foerster, O. Gagel, and W. Mahoney. 1.
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Tumours of Medulla, Pons, and Midbrain.—This long and detailed study is based on 38 cases, 25 of which were examined histologically. The various signs and symptoms and especially their frequency are discussed. One finding is that out of six mesencephalic cases three showed states of typical mania and one delirium. The authors record some important findings regarding the central diencephalo-spinal sympathetic fibres. Although removal of these tumours is not successful, the authors advise decompression, which often relieves the symptoms considerably and prolongs life. (S. L. L.)

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*Vitamin Studies in Cases of Diabetic Neuritis. W. Needles. 1,222.
Serologic Reactions in Schizophrenia : Prognostic Value. W. L. Sharp. 1,229.

Blood-Sugar Level in Petit Mal.—The abnormal electrical activity of the brain which is characteristic of grand mal epilepsy, namely, a crescendo burst of fast waves, is not sensitive to variations in blood sugar. On the other hand, the 3 per second wave and spike activity of petit mal epilepsy is decreased by high blood sugar and increased by low blood sugar. (R. M. S.)

Circulation Time in Abnormal Mental States.—The author was unable to confirm Freeman's observation that schizophrenia is characterized by an abnormality of the rate of blood flow. (R. M. S.)

Blood Choline Esterase in Myotonia.—Values for blood acetylcholine esterase in patients with myotonia congenita and myasthenia gravis fell within the same range as those of normal persons determined under the same experimental conditions. Of the nine drugs investigated, prostigmine was the only substance which significantly affected the blood esterase. The blood acetylcholine esterase in cases of myotonia congenita was not significantly changed when the clinical condition was exaggerated by epinephrine or when it was improved by quinine. (R. M. S.)

Studies in Muscle Diseases.—The balances of calcium, phosphorus, and magnesium were normal in patients with progressive muscular dystrophy and myotonia atrophica, but in a case of familial

periodic paralysis a definite defect in the metabolism of phosphorus was found. (R. M. S.)

Benzedrine Sulphate and Behaviour Problem Children.—In twelve behaviour problem children changes in the electroencephalogram were not observed to correlate with the clinical changes produced by benzedrine sulphate and phenobarbital. (R. M. S.)

Experimentally produced Pontile Hæmorrhages.—Pontile hæmorrhages, which resemble those seen in patients with space-consuming intracranial lesions, can be produced in the dog by mechanical compression of the cerebral cortex. Anoxæmia as an ætiologic factor can be ruled out. It seems likely that mechanical stretching, with subsequent rupture of units of the vascular bed, is responsible for the hæmorrhage. (R. M. S.)

Inability to Synthesize Thought in Case of Lobectomy.—Conscious inability to synthesize recognized separate thoughts is described as a new symptom of unilateral right frontal lobectomy. (R. M. S.)

Calcified Plaques in Spinal Arachnoid.—Calcification in the spinal arachnoid of man shows a predilection for the thoracic segments and a further predilection for the dorsal over the ventral surface of these levels. (R. M. S.)

Vitamin Studies in Diabetic Neuritis.—Diabetic neuritis does not appear attributable to lack of vitamin B in the diet. Reasons are discussed for considering that vascular changes in the nutrient arteries to the peripheral nerves may be responsible for the neuritis. (R. M. S.)

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*Visual Disturbances associated with Tumors of the Temporal Lobe. H. S. Sanford and H. L. Bair. 21.
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Prepsychotic Measurements of Physical and Mental Growth in a Case of Juvenile Dementia Paralytica. G. E. Gardner. 121.
Aneurysm of the Vertebral Artery. P. Bassoe. 127.

Studies in Mongolism.—From a study of thirteen cases of mongolism, Benda concludes that mongolism is associated with a pituitary disorder, particularly an insufficiency of the basophilic and chief cell system. (R. M. S.)

Visual Disturbances with Temporal Lobe Tumours.—There is definite evidence in the study of this group of tumours to indicate that the forward looping of the geniculocalcarine fasciculus, as described by Meyer, actually exists. Lesions which affect this portion of the fasciculus may produce a typical visual field defect which is of diagnostic value. (R. M. S.)

Intracranial Neoplasms and Benzidine Stain.—The vascular pattern of all the tumours of the brain studied had one feature in common, namely, an appearance suggestive of inadequacy of circulation, as compared to that of normal brain tissue. This may be one of the factors responsible for the incidence of widespread necrosis, which occurs in certain neoplasms. (R. M. S.)

Creatinine Coefficient and Creatine Tolerance Test.—The conclusion is reached that in cases of myopathy the creatinine coefficient possesses little, if any, diagnostic significance. A better test is furnished by a study of the excretion of creatine and creatinine before and after ingestion of aminoacetic acid. (R. M. S.)

Hypothalamic Nuclei in Heat Stroke.—Regulation of temperature involves the hypothalamus, but implicates a number of cell groups rather than a single centre; areas other than the hypothalamus may play a rôle. (R. M. S.)

Benzedrine Sulphate in Psychosis with Postencephalitic Parkinsonism.—Benzedrine sulphate does not seem to produce any beneficial effects on the psychotic manifestations of postencephalitis. Except for the control of oculogyric crises it is doubtful if this drug presents any advantages as compared with the drugs used in the past. (R. M. S.)

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Action Potentials of Muscles in Normal Subjects. P. F. A. Hoefer and T. J. Putnam.
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Fatal Hypoglycemia : a Clinicopathologic Study. A. L. Sahs and L. Alexander.
*Intracranial Aneurysms. C. A. McDonald and M. Korb. 298.

Recovery from Aphasia.—Three new cases in which aphasia was studied after major (left) temporal lobectomy, performed surgically in two instances and by nature (thrombotic softening) in one, and one case of minor (right) temporal lobectomy are reported. The similarity (almost identity) in the conditions of the patients in the first group in all cases so far studied places their remarkable capacity in language beyond coincidence and suggests that patients with complete loss of the major temporal lobe perform better than those with mere damage to it. Evidence is also presented that the minor temporal lobe may have considerable function in language even when the major lobe is intact. (R. M. S.)

Fibrillation in Denervated Skeletal Muscle.—The spontaneous fibrillary activity of denervated warm-blooded skeletal muscle has been shown to continue over a period commensurate with the continuing process of atrophy, persisting up to one year in all muscle grossly still recognizable as such. Under similar circumstances muscle subject to tenotomy exhibited no fibrillation. It is concluded, therefore, that with respect to the time course fibrillation may underlie the atrophy of denervated muscle but that it cannot be held accountable for the atrophy of tenotomy. (R. M. S.)

Postherpetic Neuralgia.—The pain and hyperesthesia of postherpetic neuralgia are mediated by afferent sympathetic nerves. When the neuralgia involves the head or neck it may be eliminated by removal of the stellate and several upper thoracic sympathetic ganglia on the ipsilateral side. (R. M. S.)

Estrogenic Therapy of Involutional Melancholia.—Although improvement is claimed in two out of seven cases, œstrogenic therapy in involutional melancholia does not appear to be conspicuously successful. (R. M. S.)

Intracranial Aneurysms.—This article is remarkable for the completeness of its bibliography, reference being made to 1,125 cases of saccular aneurysm of the arteries of the base of the brain. (R. M. S.)

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Syndrome d'Aphasie par Ramolissement de la Zone Lenticulaire Gauche dans une Ancienne Paralysie Générale. (The syndrome of aphasia by softening of the left lenticular zone in an old woman with paralysis agitans.) I. R. Demetrescu. 93.
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*Le Rôle du Système Diencéphalo-Hypophysaire dans le Mécanisme de la Migraine. (The rôle of the diencephalo-hypophysary system in the mechanism of migraine.) A. Salmon. 109.
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L'Importance des Vitamines et des Avitaminoses dans la Pathologie Nerveuse. (The importance of vitamins and avitaminosis in the pathology of the nervous system.) D. Paulian and I. Bistriceano. 137.
Contributions à l'Étude Hysto-pathologique et Hysto-Génétique des Myopathies Primitives. (Contributions to the histo-pathological and histogenetic study of primary myopathies.) D. Paulian and I. Bistriceanu. 143.
*Accidents Paralytiques à la Suite du Traitement Antirabique. (Paralysis following anti-rabietic treatment.) D. Paulian, C. Fortunescu, M. Cardas, and M. Chiliman. 145.
L'Électro-Encéphalographie comme Moyen d'Exploration Fonctionelle du Cerveau. (Electroencephalography as a means of functional exploration of the brain.) D. Paulian and G. G. Constantinesco. 150.

Basis of Migraine.—Migraine is due to dilatation of cerebral arterial and venous trees caused by hyperexcitability of hypophysis and hypothalamic centres acting via the carotid sinus. (W. K. S.)

Paralysis Following Antirabietic Treatment.—Case reports of polyneuritis of cranial nerves and of acute ascending myelitis following upon antirabietic treatment. (W. K. S.)

BRAIN

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*The Histology of Cerebral Œdema associated with Intracranial Tumours (with Special Reference to Changes in the Nerve Fibres of the Centrum Ovale.) J. G. Greenfield. 129.
*The Potassium Content of Muscle in Disease. J. N. Cumings. 153.
*Severe Dementia associated with Bilateral Symmetrical Degeneration of the Thalamus. K. Stern. 157.
*Neurogenic Hyperthermia (a Clinical Syndrome and Its Treatment.) T. C. Erickson. 172.
*The Sensory Innervation of the Spinal Accessory

and Tongue Musculature in the Rhesus Monkey. K. B. Corbin and F. Harrison. 191.
The Identity of Myotonia Congenita (Thomsen's Disease), Dystrophia Myotonica (Myotonica Atrophica), and Paramyotonia. O. Maas and A. S. Paterson. 198.
Clinical Investigation of Olfactory Function in Brain Tumour Patients. J. D. Spillane. 213.

Cerebral Œdema and Intracranial Tumours.—Large sections of cerebral hemispheres from 28 cases of cerebral tumour were examined histologically. Widespread changes were found in the white matter involving myelin sheaths and neuroglia. The axis cylinders were less severely affected. The changes were associated with cerebral œdema and were entirely confined to the white matter. They were most marked with secondary carcinoma and glioblastoma. (D. J. W.)

Potassium Content of Muscle.—The potassium content of muscle is abnormally low in myotonia atrophica and high in myasthenia gravis. The level was not changed by prostigmin in two normal subjects, but was raised in two myotonics and lowered in two myasthenics. (D. J. W.)

Dementia and Thalamic Degeneration.—A unique case of rapidly progressive presenile dementia associated with a selective bilateral symmetrical degeneration of the thalamus is reported. There was exclusion of the ventral, arcuate, and midline nuclei and of both geniculate bodies. The significance of this degeneration is discussed in relation to thalamo-cortical and cortico-thalamic projections. (D. J. W.)

Neurogenic Hyperthermia.—A series of clinical examples of neurogenic hyperthermia—mostly post-operative—is reported. The condition is associated with lesions of the third ventricle and brain stem, and usually consists in defective peripheral heat elimination. This can be corrected with proper management. (D. J. W.)

Sensory Innervation of Spinal Accessory and Tongue Musculature.—Degeneration and oscillographic experiments in *Macacus Rhesus* show that proprioceptive fibres from the accessory musculature arise in the dorsal root ganglia of C2, 3, and 4. They are carried in the corresponding ventral roots to anastamose with the accessory nerve, which is entirely motor. Proprioceptive fibres from the tongue arise in the dorsal root ganglia of C2 and travel in the hypoglossal nerve. (D. J. W.)

CLINICAL SCIENCE

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*Hyperpnœa in Heart Failure. J. McMichael. 19.
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*Observations relating to Referred Pain, Viscero-Motor Reflexes, and Other Associated Phenomena. T. Lewis and J. H. Kellgren. 47.
A Note on the Serum Sodium Level in Patients suffering from Tuberculosis. J. O. Westwater, D. Stiven, and R. C. Garry. 73.
*Ocular Effects of Sympathetic Stimulation in Man. E. E. Pochin. 79.
*The Mechanism of Lid Retraction in Graves' Disease. E. E. Pochin. 91.

Hyperpnœa in Heart Failure.—Evidence of jugular venous oxygen content suggests that cerebral blood flow is subnormal in hyperpnœic cardiac subjects. (W. M. H.)

Referred Pain and Viscero-Motor Reflexes.—By stimulation of interspinous ligaments the phenomena accompanying visceral disease usually described as "referred" may be mimicked. Pain of visceral and of somatic origin cannot be distinguished. In the decapitated cat viscero-motor reflexes depend on stimulation of the mesentery. Injury, distension, or contraction of the bowel yield a rise in blood pressure. (W. M. H.)

Ocular Effects of Sympathetic Stimulation.—Stimulation of the cut cervical sympathetic causes retraction, and section causes relaxation of the upper and lower lids in man. (W. M. H.)

Lid Retraction in Graves' Disease.—In Graves' disease retraction of the upper eyelid resembles that caused by spasm of the levator palpebræ superioris. Sympathetic overactivity is not the cause of the lid retraction. (W. M. H.)

L'ENCÉPHALE

Vol. 34 (1). No. 2. February 1939.

*Sclérose Tubérose à Forme Maligne. (Tuberose sclerosis of malignant type.) L. Marchand, M. Brisset, and J. Maillefer. 57.
*Le Syndrome Catatonique des Psychoses Cannabiques Aiguës. (Catatonia in acute psychoses of toxic origin.) P. Scouras. 78.
Lacunes et Images Radiologiques Lacunaires du Crâne. (Lacunæ and radiological lacunar images in the skull.) H. Roger and M. Schachter. 86.

Tuberose Sclerosis.—Congenital idiocy in a boy aged 7½ was associated with epilepsy, generalized muscular atrophy, and paresis, with cutaneous malformations varying from sebaceous adenomas to neurofibromas and epitheliomas. Pathological examination revealed a generalized

neuroglial overgrowth in the cortex, with neuronic degeneration and formation of sclerotic plaques in the subependymal layers of the 3rd and 4th lateral ventricles. Tumour formations included an astrocytoma of the right occipital cortex, endotheliomas in the choroid plexus, renal neurofibromas, and a cardiac rhabdomyoma. The disease was heredofamilial. (W. K. S.)

Catatonia in Psychoses of Toxic Origin.—Conditioned reflexes were assumed to be responsible for the induction of catatonic postures in psychoses produced or aggravated by chronic toxicomania. (W. K. S.)

Vol. 34 (1). No. 3. March 1939.

La Cataplexie. Étude Physio-Pathologique et Pathogénique. (Cataplexy. Physio-pathological and pathogenic study.) P. Verger and J. Lafon. 121.

*Des Déterminations Pharmacologiques de l'Histamine dans le Sang des Schizophrènes et de Divers Sujets de Contrôle. (Pharmacological determinations of histamine in the blood of schizophrenics and of various control subjects.) W.-A. den Hartog Jager. 149.

Un Cas de Pachyméningite Hémorragique Interne. (A case of internal hæmorrhagic pachymeningitis.) H. Calude and J. Cuel. 161.

Histamine Determination in the Blood of Schizophrenics.—The blood content of histamine shows no elevation in cases of schizophrenia. (W. K. S.)

JOURNAL BELGE DE NEUROLOGIE ET DE PSYCHIATRIE

Vol. 39. No. 4. April 1939.

*La Thérapeutique de la Schizophrénie par les Convulsions. (The treatment of schizophrenia by convulsions.) L. von Meduna. 227.

Maladie d'Alzheimer ayant Évolué comme une Maladie de Pick. (Alzheimer's disease having an evolution similar to Pick's disease.) P. Divry. 238.

Tumeur Frontale et Oligophrénie. (Frontal tumour and oligophrenia.) C. Massaut. 246.

Origine Toxique de la Paralysie dans le Syndrome de Guillain-Barré. (Toxic origin of Guillain-Barré's paralysis.) Heernu. 250.

Le Traitement de la Démence Précoce par l'Insulinothérapie et la Convulsivothérapie Combinées. (Treatment of dementia præcox by combined insulin and convulsive therapy.) H. Baonville, J. Ley, A. and J. Titeca. 255.

*Études Électrencéphalographiques dans l'Épilepsie. (Electro-encephalographic studies in epilepsy.) O. Sager and A. Kreindler. 265.

Treatment of Schizophrenia by Convulsions.—Statistics of results in 46 European clinics are reported. (W. M. H.)

Electro-Encephalographic Studies in Epilepsy.—The groupage of waves in the electro-encephalogram in epilepsy resembles those of chronic decorticated dogs under evipan and of atropinized rabbits. (W. M. H.)

Vol. 39. No. 5. May 1939.

*Étude sur le Mode d'Extension et l'Histo-Pathologie des Trypanosomiases Expérimentales. (Experimental trypanosomiasis.) L. van Bogaert. 295.

Contribution Anatomo-Expérimentale à l'Étude des Commissures Supra-Optiques. (Anatomo-experimental study of the supra-optic commissures.) M. A. Gerebtzoff. 320.

De Certains Accidents au Cours de la Cure de Cardiazol chez les Schizophrènes. (Certain accidents in the course of cardiazol treatment of schizophrenia.) M. Gross and G. Gross-May. 336.

Polynévrite Consécutive à un Traitement d'Ulirone. (Polyneuritis following treatment with Ulirone.) M. Radermecker. 349.

Experimental Trypanosomiasis.—From the blood vessels the trypanosomes penetrate the parenchyma, but in some cases the infection spreads by the cerebrospinal fluid. Intense perivascular infiltration is found with change in the nerve cells especially in the frontal area, hippocampus, and base of the brain. The white matter shows little change save in the vicinity of necrotic foci in the grey. (W. M. H.)

JOURNAL OF CLINICAL INVESTIGATION

Vol. 18. No. 4. July 1939.

*Responses of Normal Subjects and of Patients with Diabetes Insipidus to Water and Salt Ingestion. H. L. White and T. Findley. 377.

Lactic Acid Production during Rest and after Exercise in Subjects with Various Types of Heart Disease with Special Reference to Congenital Heart Disease. P. Hallock. 385.

The Use of CO_2 Inhalation as a Test of Circulation Time. R. Gubner, S. Schnur, and J. H. Crawford. 395.

Clinical Studies of the Blood Volume. VI. Changes in Blood Volume in Pernicious Anemia in Relation to the Hematopoietic Response to Intramuscular Liver Extract Therapy. J. G. Gibson. 401.

A Secretory Depressant in Gastric Juice of Patients with Pernicious Anemia. A. Brunschwig, J. van Prohaska, T. H. Clarke, and E. Kandel. 415.

Sulfapyridine, Sulfanilamide, and Specific Antiserum in Experimental Type III Pneumococcic Infection. F. B. Cooper, P. Gross, and M. Lewis. 423.

On Vagal and Extravagal Factors in Cardiac Slowing by Digitalis in Patients with Auricular Fibrillation. H. Gold, N. T. Kwit, H. Otto, and T. Fox. 429.

Mechanism of the Arterial Hypertension Induced by Paredrinol (*a*-N-Dimethyl-*p*-Hydroxyphenethylamine). E. A. Stead and P. Kunkel. 439.

Treatment of Addison's Disease with Desoxy-Corticosterone Acetate, a Synthetic Adrenal

Cortical Hormone. (Preliminary Report.) G. W. Thorn, R. P. Howard, and K. Emerson. 449.
Proceedings of the Thirty-First Annual Meeting of the American Society for Clinical Investigation held in Atlantic City, N.J., May 1, 1939. 469.

Water and Salt Ingestion in Diabetes.—The response in renal function in normal subjects and four patients with diabetes insipidus to sodium chloride by mouth and pitressin subcutaneously has been studied. Apart from some delay for a few hours in excreting sodium chloride no significant difference was found between these two groups. (J. N. C.)

JOURNAL OF COMPARATIVE NEUROLOGY

Vol. 70. No. 3. June 1939.

The Cerebral Cortex of *Rhea Americana*. E. H. Craigie. 331.
Notes on the Comparative Anatomy of the Sensory Areas of the Vertebrate Inner Ear. J. K. Weston. 355.
Studies of the Size of the Cells in the Cerebral Cortex. III. The Striate Area of Man, Orang, and Cebus. G. von Bonin. 395.
Neuronophagia in the Brain of the Mouse as a Result of Inanition, and in the Normal Ageing Process. W. Andrew. 413.
Studies in the Physiology of the Embryonic Nervous System. II. Experimental Evidence on the Controversy over the Reflex Theory in Development. Z. Y. Kuo. 437.
*The Effects of Combined Red Nucleus and Pyramidal Lesions in Cats. B. H. Evans and W. R. Ingram. 461.
*The Development of Behaviour of Fœtal Sheep. J. Barcroft and D. H. Barron. 477.

Combined Red Nucleus and Pyramidal Lesions.—In cats destruction of the red nuclei or interruption of the rubro-spinal tracts causes dysmetria, increased extensor tonus, and defective hopping and placing reactions. Partial section of the pyramid causes varying increase in extensor tonus and deficiency in the postural reactions of the contra-lateral limbs. Compensation is rapid. Both pyramidal and rubro-spinal systems regulate muscle tonus and movement in cats. Each may compensate for the other, but the means of compensation for injury to both is unknown. (W. M. H.)

Behaviour in Fœtal Sheep.—In the fœtus of sheep the first responses to stimulation of peripheral sensory nerves are restricted in the amount of musculature involved. Later responses are more extensive, especially on stimulation of nerves to the head region. (W. M. H.)

JOURNAL OF MENTAL SCIENCE

Vol. 85. No. 357. July 1939.

The Physiological Pathology of the Anterior Pituitary. (General Review.) M. Reiss. 619.
The Modern Psychiatric Approach to Crime. W. N. East. 649.
Blood Groups in Health and in Mental Disease. J. C. Thomas and E. J. C. Hewitt. 667.
Serum Iso-Agglutinum Titres in Health and in Mental Disease. J. C. Thomas and E. J. C. Hewitt. 689.
Insulin Shock Therapy. I. Carbohydrate Metabolism in Schizophrenia (Preliminary Observations). J. C. Thomas, B. Gilsenan, and E. J. C. Hewitt. 696.
*Sterilization Policy, Economic Expediency, and Fundamental Inheritance, with Especial Reference to the Inheritance of the Intelligence Quotient. W. E. Southwick. 707.
*The Genetics of Phenylpyruvic Oligophrenia (a contribution to the Study of the Influence of Heredity on Mental Defect.) G. A. Jervis. 719.
Choreoathetosis and Infracortical Nervous Mechanisms. W. F. Menzies. 763.
A Variability Study of the Normal and Schizophrenic Occipital Alpha Rhythm. II. The Electro-Encephalogram and Imagery Type. M. A. Rubin and L. H. Cohen. 779.
Further Observations on Temporary Treatment. L. Minski. 784.
Blood-Pressure in Cardiazol Epilepsy. E. Guttmann and F. Reitmann. 787.
Psychic and Somatic Reactions to Subconvulsive and Convulsive Doses of Triazol. J. B. Dynes and H. Tod. 796.

Sterilization Policy and Intelligence Quotient.—Sterilization is justifiable where the germ-plasm is distinctly deleterious to the welfare of society, as in the group of institutionalized parents who represent the aggregation of allelomorphic pairs occurring in a homozygous low I.Q. condition. (W. K. S.)

Genetics of Phenylpyruvic Oligophrenia.—Analysis of sibships of 213 cases of phenylpyruvic oligophrenia pointed to a single autosomal recessive gene as the determining genetic factor. (W. K. S.)

JOURNAL OF NERVOUS AND MENTAL DISEASE

Vol. 89. No. 6. June 1939.

"Kate the Curst." J. W. Draper. 757.
Psychological "Repression" and Neurological "Inhibition." R. R. Grinker. 765.
Cystic Hydrops of the Pineal Gland. A. F. Liber. 782.
Genealogical Studies in Huntington's Chorea. T. T. Stone and E. I. Falstein. 795.
Schizophrenia with Cardiazol in Convulsant Doses. H. Dalgado. 810.

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*A Specific Motility Psychosis in Negro Alcoholics. S. Parker, P. Schilder, and H. Wortis. 1.
Juvenile General Paralysis. J. L. Hoffman and A. M. Duval. 19.
Tumor of the Base of the Brain simulating an Aneurysm of the Internal Carotid Artery. L. E. Grimberg and D. Arbuse. 22.
A Study of the Influence of Heterophile Antigen in Nervous and Mental Disease. E. W. Lazell. 31.
Familial Lateral Sclerosis. G. E. Price. 51.

Motility Psychosis.—Out of a large number of alcoholic psychoses, these authors have described eight cases of a specific type, which they call a "specific motility psychosis." Seven of these occurred in negroes. The syndrome is characterized by clouding of consciousness, hallucinations, mannerisms, and playfulness. The motor signs consist of rhythmic iteration, retropulsion, falling backwards, rigidities, increased divergence of the anus, and turning about the longitudinal axis. The authors attribute the motility to a disturbance in the psycho-motor attitude of the patient. A ninth case has been recorded. This patient was a negro schizophrenic who was alcoholic. The similarity between catatonic schizophrenia and this syndrome was pointed out. The alcoholism was held to be incidental in this patient. (I. G. J.)

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A Paradoxal Tonic Contraction of the Eye Muscles by Reflex Irritation. L. I. Omorokov. 47.
Materials on Comparative Epidemiology of the Spring-Summer Encephalitis (Materials of 1933–1937.) A. G. Panov. 50.
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The Clinic of the Nervous System Involvement after Toxic Doses of Plazmocid. N. S. Rojaeva. 115.
Affection of the Eyes and Nervous System on Incorrect Dosage of Plazmocid. S. M. Brailovsky and S. M. Kuklin. 123.
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The Pupil Reflex. N. S. Mendelson. 131.

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The Bioelectrical Manifestations in the Ocular, Motor, and Parietal Sections during Eye Enucleation in a Rabbit. S. A. Sarkisov. 11.
The Pathogenesis of Subarachnoid Hemorrhage. E. L. Venderovich. 20.
On the Treatment of Pain by Resection of the Fibres which leave the Cerebrospinal Nodes in Peripheral Direction (" Extra-ganglion Resection " according to Molotkov's Method). L. A. Shilnikov. 27.
The Problems of Pathogenesis of the Progressive Muscular Dystrophy. I. The Creatin-Creatinin Metabolism. L. I. Shargorodsky. 34.
Some Deductions on Basis of Further Study of the Pathogenesis and Treatment of Schizophrenia. II. The Significance of Biologic Therapy in the Study of the Clinic of Schizophrenia. A Practical Classification of Schizophrenia from the Standpoint of Its Reaction to the Various Therapeutic Procedures. P. F. Malkin. 68.
On the Psychopathology of the Korsakov's Syndrome. G. B. Abramovitch. 80.
Acute Hallucination : Paranoid Conditions connected with Induced Sleeplessness. N. M. Krohl and M. A. Bourkovskaja. 90.
On the Development of the Cortex Structures in Man. I. A. Stankevich. 99.
On the Mechanism of the Auricular-Temporal Syndrome (An Attempt of a Physiologic Analysis). F. P. Lampert. 107.
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The Peculiarities of the Optical Visions in the Hallucination-Paranoid and Confabulatory Syndromes in Schizophrenic Patients. N. P. Bogush. 123.
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On the Activity of the Sweat Glands of the Face. N. I. Boot. 144.

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The Clinic and Psychopathology of Hallucination Disturbances, developing in Schizophrenic Patients in the Course of their Treatment with Narcotic Sleep. V. A. Giliarovsky. 5.
Experimental Mescalinization in the Topical Diagnosis of Brain Affections. D. E. Stolbun. 21.
The Venous Pressure in Patients of the Neuro-Surgical Section. N. N. Ovchininsky. 36.
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Functional Disturbances in the Vestibular Apparatus caused by Injury with the Electric Current. L. I. Alexandrova and A. S. Aivazov. 61.
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The Differential Diagnosis between Vascular and Inflammatory Processes in the Brain (Embolia or

Encephalitis). G. G. Sokoljansky and D. M. Gastev. 70.

Changes in the Nervous System caused by Malarial Coma. K. A. Kunakov. 75.

The Lange Reaction in the Cerebro-Spinal Liquor in Neuro-Malaria. N. F. Vorobjev. 80.

A Case of Hypernephroma with Multiple Metastasis into the Brain and Spinal Column. R. J. Ponizovskaya. 85.

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*Cerebral Blood Flow during Induced Epileptiform Seizures in Animals and Man. W. Penfield, K. von Sántha, and A. Cipriani. 257.

Rôle of the Sympathetic System in Reflex Dilatation of Pupil. B. Ury and E. Gellhorn. 268.

Effects of Hypoglycemia and Pentobarbital Sodium on Electrical Activity of Cerebral Cortex and Hypothalamus (Dogs). H. Hoagland, H. E. Himwich, E. Campbell, J. F. Fazekas, and Z. Hadidian. 276.

*Cortical Action Potentials during Anesthesia. H. K. Beecher and F. K. McDonough. 289.

The Acoustic Area of the Cerebral Cortex in the Cat. A Combined Oscillographic and Cyto-architectonic Study. F. Bremer and R. S. Dow. 308.

*Factors for Facilitation and Extinction in the Central Nervous System. J. G. Dusser de Barenne and W. S. McCulloch. 319.

*Control by the Central Nervous System of Rectal Smooth Muscle. O. R. Langworthy and S. J. Rosenberg. 356.

Cerebral Blood Flow during Induced Epileptiform Seizures.—In man and in animals fits induced by electrical stimulation of the cortex are accompanied by an increase in local circulation of the cortex and deeper parts as gauged by thermo-junctions. (W. M. H.)

Cortical Action Potentials.—The histological and physiological boundaries of the acoustic area in the cat as described by Kornmüller have been confirmed. (W. M. H.)

Facilitation and Extinction in C.N.S.—Analysis of the parameters of cortical stimulation and the latency and amplitude of motor responses in macaques under dial anæsthesia indicates that the factors for facilitation are : (1) hyperactivity, yielding increased summation ; (2) negative voltage drift associated with decrease in threshold of neurones previously involved ; and (3) probably increase in *p*H. For extinction factors are : (1) hypoactivity ; (2) positive voltage drift ; and (3) decrease in *p*H. A new approach to reciprocal innervation comes from the demonstration of the reversal of a cortical focus and the influence of imbalance between extensor and flexor cortical foci on the knee jerk. (W. M. H.)

Rectal Smooth Muscle and Control by C.N.S.—In the cat after transection of the brain stem just cephalic to the acoustic colliculi the smooth muscle of the rectum becomes hyperactive to stretch stimuli. After lower section through the medulla the stretch responses are lost. (W. M. H.)

JOURNAL OF PHYSIOLOGY

Vol. 96. No. 1. June 1939.

The Effect of Stretching and of Stimulation on the Weight, Total Base, and Sodium Concentration of the Anterior Retractor of the Byssus of *Mytilus Edulis*. I. Singh. 1.

The Indirect Determination of the Gas Tensions in the Mixed Venous Blood. I. F. S. Mackay. 9.

The Gastric Secretions in Experimental Hypochloræmia. A. Lyall and B. M. Nicol. 21.

*The Relation between Concentration of Visual Purple and Retinal Sensitivity to Light during Dark Adaptation. R. Granit, A. Munsterhjelm, and M. Zewi. 31.

The Relation between Force and Speed in Muscular Contraction. B. Katz. 45.

The Resistance of Nerve in Relation to Interpolar Length. J. F. Danielli. 65.

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*The Influence of Urea and of Change in Arterial Pressure on the Oxygen Consumption of the Isolated Kidney of the Dog. K. Kramer and F. R. Winton. 87.

*The Effect on the Intestine of the Substance liberated by Adrenergic Nerves in a Rabbit's Ear. J. H. Gaddum, C. S. Jang, and H. Kwiatowski. 104.

Visual Purple and Retinal Sensitivity.—The rise in sensitivity of the dark adapted eye does not have a close linear function to the curve of the visual purple regeneration in terms of density values. Zero sensitivity is reached with 40 per cent. visual purple, which lends support to the theory of some intermediate process. (W. K. S.)

Oxygen Usage of Kidney and Diuresis.—A transient decrease in arterio-venous O_2 difference is seen only if diuresis induced by increase in arterial pressure within physiological limits or in urea content of perfusion fluid. There is no simple relationship between urine formation and renal oxygen consumption. (W. K. S.)

Substance Liberated by Adrenergic Nerves.—Stimulation of the vasomotor nerves in a rabbit's ear liberates a substance which inhibits a fowl's rectal cæcum and has specific colour reaction of adrenaline. (W. K. S.)

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*The Effect of Forced Breathing on the Motor Chronaxie. B. Dijkstra and M. N. J. Dirken. 109.
*The Origin and Nature of Ganglion After-Potentials. D. P. C. Lloyd. 118.
*Effect of Clotting and of Addition of Histamine on Its Distribution in Blood. G. V. Anrep, G. S. Barsoum, M. Talaat, and E. Wieninger. 130.
The Release of Histamine by Isolated Smooth Muscle. N. Ambache and G. S. Barsoum. 139.
*Some Effects of Stimulation of Sympathetic Nerves and Injection of Pressor Drugs in Adrenalectomized Cats. C. W. J. Armstrong, R. A. Cleghorn, J. L. A. Fowler, and G. A. McVicar. 146.
Rotatory Movements of the Apex of the Exposed Mammalian Heart. K. J. Franklin. 164.
The Effect of Tetanus Toxin on the Choline Esterase Activity of the Muscles of Rats. E. Martini, C. Torda, and A. Zironi. 168.
The Absorption of Monosaccharides from the Large Intestine of the Rat under Urethane Anæsthesia. J. N. Davidson and R. C. Garry. 172.
Changes in Elasticity of Mammalian Muscle Undergoing Rigor Mortis. E. C. Bate Smith. 176.
The Distribution of Sodium Between the Aqueous Humour and Blood Plasma of Cats. H. Davson. 194.
Nerve Excitation by High-Frequency Alternating Current. B. Katz. 202.
*The Effect of Temperature upon Dorsal Root Potentials in the Frog. C. B. Finley. 225.

Forced Breathing and Chronaxia.—In rabbits hyperventilation caused a rise in the motor chronaxie, which was due to alteration of the skin impedance. (W. K. S.)

Ganglion After-Potentials.—The origin of after-potentials in the inferior mesenteric ganglion lies in the cell body and not in presynaptic structures. The form and time-course of these after-potentials agree, within the limits of synaptic stimulation, with the excitability cycle of the cell body and also are analogous to the after-potentials of peripheral nerve. (W. K. S.)

Distribution of Histamine in Blood.—The histamine equivalents of the white cell layer in human and in rabbit centrifuged and unclotted blood are 50–60 per cent. of the total histamine content. On clotting the equivalent of the erythrocytes is unchanged, that of the serum is of the same value as the plasma, whilst from the fibrin can be recovered the entire histamine content of the white cell layer. (W. K. S.)

Sympathetic Nerve Stimulation in Adrenalectomized Cats.—Impairment of the vascular response to splanchnic stimulation in adrenalectomized cats is not due to diminution in blood volume or to loss of adrenal medulla, but a contributing factor may be exhaustion of the chemical mediator at the neuromuscular synapses. (W. K. S.)

Dorsal Root Potentials in Frog.—The high-temperature coefficient of the latency of the dorsal root potentials lends support to the conception of its origin as being in the large, long-lasting depolarization of the fine primary terminations. The fact that the rise to maximum and the fall of the potential change have lower temperature coefficients suggests the involvement of more complex physiological factors. (W. K. S.)

PHYSIOLOGICAL REVIEWS

Vol. 19. No. 3. July 1939.

The Effects of Extirpation on Higher Brain Processes. C. F. Jacobsen. 303.
The Detoxication of Carbocyclic Compounds. L. Young. 323.
Coenzymes. C. A. Baumann and E. J. Stare. 353.
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Aplastic Anemia arising during Metrazol Treatment of Schizophrenia—Report of a Fatal Case. J. Epstein. 419.
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The Serum Lipids in Schizophrenia. L. O. Randall and L. H. Cohen. 441.
Psychosis with Syphilitic Meningo-Encephalitis (General Paresis) Eight Months after Chancre. M. Zeifert. 449.
Psychosis with Psychopathic Personality. W. E. Cudmore. 457.
The Syndrome of Acute (Alcoholic) Hallucinosis. G. M. Davidson. 466.
Metrazol Therapy in Manic-Depressive and Involutional Psychoses. M. Zeifert. 498.
A Theory for the Cause of Deaths in Acutely Disturbed Mental Patients. W. A. Thompson. 503.
Symptoms and Previous Personality in Prison Psychoses. S. C. Karlan. 514.
The Psychic Aspects of Bronchial Asthma. R. B. Sampliner. 521.
*Disturbances in the Reticulo-Endothelial System during the Course of Metrazol Treatment. L. Wender and M. D. Epstein. 534.
A Behaviour Problem—Runaways. B. H. Balser. 539.
A Statistical Study of 1,140 Dementia Præcox Patients treated with Metrazol. H. M. Pollock. 558.
Discussion. C. H. Bellinger. 569.
Listening to a Staff Conference. J. Chassell. 574.

Reticulo-Endothelial Disturbances during Metrazol Treatment.—Three cases are reported which exhibited during metrazol treatment enlargement of certain lymphatic glands with blood changes approximating to those of leucopenic leukemia. Blood pictures of this type are found in most cases within the first six hours of treatment, with a return to normal within 24 hours. Blood smear examination within 24 hours is recommended in all cases. (G. M. F.)

REVUE NEUROLOGIQUE

Vol. 71. No. 5. May 1939.

*Hypertrophie Musculaire Généralisée de l'Adulte à Constitution Rapide et Myxœdème Fruste Concomitants, Cliniquement Guéris par le Traitement Thyroïdien. (Generalized muscular hypertrophy of rapid onset associated with myxœdema in an adult, clinically improved by thyroid treatment.) P. Mollaret and J. Sigwald. 513.

Hypertrophie Musculaire Généralisée de l'Adulte à Constitution Rapide et Myxœdème Fruste Concomitants, Electriquement très Améliorés par le Traitement Thyroïdien. (Generalized muscular hypertrophy of rapid onset in an adult. Electrical reactions much improved by thyroid treatment.) G. Bourguinon. 548.

Muscular Hypertrophy in Myxœdema.—A case of apparent muscular hypertrophy in myxœdema is described and the literature reviewed. (W. M. H.)

Vol. 71. No. 6. June 1939.

Spasme Clonique Localisé aux Muscles Innervés par le Sciatique Poplité Externe et Calmé par le Réchauffement des Jambes. (Localized clonic spasm of the muscles innervated by the external popliteal nerve and relieved by warming of the limb.) A. Souques. 673.

Sur la Sclérose Inflammatoire de la Substance Blanche des Hémisphères (Spielmeyer). (Contribution à l'Étude des Scléroses Diffuses non Familiales.) (Inflammatory sclerosis of the cerebral white matter.) L. van Bogaert and J. de Busscher. 679.

La Tension Artérielle Rétienne dans les Tumeurs Intracraniennes : son Importance pour le Diagnostic Topographique, et son Rôle dans la Formation de la Stase Papillaire. (Retinal arterial pressure in cerebral neoplasms.) G. de Morsier, M. Monnier, and E. B. Strieff. 702.

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Vol. 12. No. 2. April 1939.

*Adeno-Carcinoma Metastatico del Cervello. Contributo Anatomo-Clinico allo Studio delle Localizzazioni al Corpo Striato. (Metastatic adeno-carcinoma of the brain. Anatomical and clinical contribution to the study of localization in the corpus striatum.) R. Pasqualini. 93.

*Gli Anticorpi nel Sangue e nel Liquor Dopo la Vaccinazione per Via Endovenosa ed Endorachidea. (Antibodies in the blood and c.s.f. after intravenous and intrathecal vaccination.) G. Sogliani. 122.

*Sulle Calcificazioni dei Plessi Corioidei. (Calcification of the choroid plexus.) G. Fattovich. 136.

*Carcinoma Metastatico Multiplo della Volta Cranica : Sindrome Neuro-Psichica da Compressione. (Multiple metastatic carcinomata of the cranial vault. A neuropsychiatric syndrome from compression.) G. Francioni and A. Comellini. 149.

Metastatic Adeno-Carcinoma of Brain.—A case is illustrated of a secondary tumour in the brain of a woman of 57. Nodules were found in the right occipital lobe and in the head of the left caudate nucleus. Clinically there was a complex symptomatology characterized by hypertonic crises of the right side of the body accompanied by transitory paralysis of the right 3rd nerve and a pyramidal type of paralysis of the left limbs, also transitory. The author maintains that such symptomatology, the mechanism of which he discusses, should only be attributed to a blastomatous nodule of the caudate nucleus. (R. G. G.)

Antibodies in Blood and C.S.F.—The author has conducted a comparative study of the concentration of antibodies in the blood serum and in the c.s.f. of subjects into whom typhoid bacilli and B. coli (5 and 50 million) were introduced by various routes, hypodermically, intravenously, and intrathecally. The results obtained, in accordance with previous findings in animals, confirm the greater efficacy of the introduction of antigens intrathecally compared to other routes for the production of antibodies in the blood. He thinks it is possible to produce small quantities of antibody in the central nervous system which may be discovered in the c.s.f. (R. G. G.)

Calcification of Choroid Plexus.—The author illustrates a case of diffuse calcification of the choroid plexus in both lateral ventricles, which resulted in a mass of considerable volume clearly observable at P.M. examination. He describes the histological report. (R. G. G.)

Metastatic Carcinomata of Cranial Vault.—The authors describe a case of multiple carcinomata in the bones of the cranial vault whose primary focus was an epithelioma of the lower lip. The cranial metastases, which were enormously developed, did not invade either the brain or the meninges. Hence the neuropsychiatric syndrome (right hemiplegia, motor and sensory aphasia, and dementia) was caused solely by pressure of the mass on the left hemisphere. The authors consider this an important case, since they have not been able to find in the literature any description of a case of secondaries in the cranial vault from an epithelioma of the lower lip. (R. G. G.)

Vol. 12. No. 3. June 1939.

*I Tumori Perlacei Cerebrali. (Pearly tumours of the brain.) A. Baleari. 195.
*Contributo allo Studio delle Sindromi Neurologiche da Impressione Basilare dello Scheletro. (Contribution to the study of the neurological syndrome consequent on the pressure of the base of the skull.) D. Alessi. 218.

Pearly Tumours of the Brain.—Three cases of pearly tumours (epithelial rests) are described of which two were in the tempero-parietal region and the other in the supracellar region invading the third ventricle. Clinical observations were correlated with histological examination. After a revision of the cases described in the literature and the theories of origin of these tumours, the author discusses his own histological findings. (R. G. G.)

Basilar Pressure of the Skull.—A case of basilar pressure of the skull is described determined by a particular shape of the head, which was associated at the age of 22 with a complex neurological syndrome mainly sensory in character. There was an intrabulbar lesion and not, as is maintained in respect of other cases in the literature, a dislocation of the odontoid process. (R. G. G.)

RIVISTA DI PATOLOGIA NERVOSA E MENTALE

Vol. 53. No. 2. March–April 1939.

*Su di un Caso di Ependimoma del IV Ventricolo. (Ependymoma of the 4th ventricle.) G. M. Fasiani and C. Berlucchi. 171.
*L'Acetilcolinesterasi nel Liquido Cefalo-Rachidiano. (Acetylcholin esterase in c.s.f.) O. Pinotti and L. Tanfani. 181.
*Contributo allo Studio delle Manifestazioni Psicopatologiche delle Popolazioni dell'Impero. 1. Cherbe—Malattia dei Diavoli. (Psychological manifestations among the Empire's population. 1. "Cherbe"—possessed with devils.) S. Brambilla. 187.
*Sull-Uso degli Estratti di Sostanza Cerebrale per la Diagnosi e la Prognosi delle Forme Metaluetiche. (Extracts of brain substance used in the diagnosis and prognosis of parasyphilis.) E. Dossi. 207.
*Considerazioni sul Periterminalreticulum sul Terminalreticulum e su Altri Aspetti Nervosi Espansionali Periferici, Anche nei Reguardi della Teoria del Neurone. (Views upon the periterminal and terminal reticula and other examples of peripheral nerve expansions in relation to the theory of the neurone.) F. Rossi. 216.
*Cisti Idatidea del IV Ventricolo con Leptomeningite Otto-Chiasmatica. (Hydatid cysts in the 4th ventricle with leptomeningitis in the region of the optic chiasma.) A. Rubino. 249.
*Terapia Iodica Endodurale nella Leptomeningite Otto-Chiasmatica e nell' Atrofia Ottica Tabetica (Leptomeningite Otto-Chaismatica Tabetica ?). (Endodural iodine therapy in lepto-meningitis of the optic chiasma and tabetic optic atrophy (tabetic lepto-meningitis of the optic chiasma ?)) A. Rubino. 288.
*Sull'Alterazione della Colesterolemia Negli Epilettici e sua Possibile Etiopatogenesi. (Alteration of cholesterin content of the blood in epileptics, and the possibility of its ætiological significance.) G. Gomirato. 319.
*E la Sindrome di Adie dovuta a Carenza di Vitamina B ? (Is Adie's syndrome due to lack of vitamin B ?) D. Bettini. 331.

Ependymoma of 4th Ventricle.—A case of extra ventricular ependymoma of the 4th ventricle is described, which is of particular interest in respect of: (1) the remarkable extension of segmental symptoms related to the cervical cord; (2) the findings of cisternal puncture (failure to obtain fluid); (3) the favourable outcome of operation. (R. G. G.)

Acetylcholin Esterase in C.S.F.—It is possible to demonstrate the presence of acetylcholin esterase in the human cerebrospinal fluid by biological tests. It is constantly present, but its concentration varies considerably from individual to individual. The variation in the activity of fluid in respect of functions depending on the esterase are parallel to those which have been verified in the plasma of the same subjects. (R. G. G.)

Psychological Manifestations.—There is frequently observed amongst Abyssinians a particular psychic manifestation characterized by convulsive attacks in which the pantomimic manifestations reveal a partially conscious defensive attitude against the influence of devils (Cherbe) which possess the native in certain circumstances. Besides the social importance due to the remarkable frequency of this phenomenon, it is interesting from a psychopathological point of view as an expression of a psychogenic reaction implanted on a primitive mentality which shows parallelism with specific manifestations of the primitive and archaic thought-processes of the schizophrenic. (R. G. G.)

Extracts of Brain Substance in Parasyphilis.—Contrary to the opinion of several authorities quoted from the literature, the author, referring to a series of his own researches on this subject, denies the utility of these methods in the differential diagnosis between cerebrospinal syphilis and parasyphilis. Also he denies their use in prognosis based on the behaviour of the complement fixation tests with these substances. (R. G. G.)

Peripheral Nerve Expansions and Theory of Neurone.—A summary of the principal researches undertaken in the last 20 years in the field of the peripheral nervous system particularly in relation to the sympathetic segments. The author has analysed and criticized the findings and conclusions of the schools of Stöhr and Boeke in regard to the terminal reticulum and especially the periterminal reticulum in relation to the theory of the neurone. His own and other Italian work seems to help to clarify this field of research. (R. G. G.)

Hydatid Cysts and Leptomeningitis.—In life the symptomatology was confined to the clinical expression of internal hydrocephalus with an increase of C.S.F. pressure, suggesting a tumour of a median ventricle. The clinical course was terminated by unexpected death. There was considerable distension of the third ventricle and an adhesive leptomeningitis round the optic chiasma which explained the ocular symptoms, which had in life caused suspicion of an inflammatory process below the chiasma. Histological examination showed a small celled infiltration with in some places a true barrier of marginal inflammation. With regard to the pathogenesis of the leptomeningitis of the optic chiasma, two factors were of importance—the severe hydrocephalus of the third ventricle and the toxic factors due to the presence of hydatid cysts. (R. G. G.)

Endodural Iodine in Leptomeningitis.—After discussing the inconvenience of surgical and medical (intravenous iodine) therapy, he describes the results of a new treatment by the endodural injection of iodine. This treatment gave the optimum results in two cases of leptomeningitis round the optic chiasma with serious ocular symptoms. But in tabetic optic atrophy it gave practically negative results. This method is therefore useful in diagnosing between leptomeningitis round the optic chiasma due to nasal sinusitis and that due to tabes, and may be also useful in differentiating between a tumour and an inflammatory process in the region of the sella. (R. G. G.)

Cholesterin Content of Blood in Epileptics.—Hypocholesterinæmia was found in twelve cases of epilepsy in the period of remission and in that near the attack. This was especially the case in a subject whose fits were provoked by hyperventilation. The author thinks this may be due partly to an alteration of liver function and partly to a fixation of cholesterol in the tissues as a result of alkalosis. (R. G. G.)

Adie's Syndrome and Vitamin B Deficiency.—A case of Aide's syndrome (tonic pupils and absent tendon reflexes) is described in which hypodermic administration of vitamin B resulted in a restoration of both pupils and tendon reflexes to normal within a month. In some cases, therefore, Adie's syndrome may be due to a slow, benign polyneuritis kept up by lack of vitamin B. (R. G. G.)

Vol. 53. No. 3. June 1939.

*Contributo alla Conoscenza della Cosidetta Forma Poliomielitica Pura della Sclerosi Laterale Amiotrofica. (Contribution to the knowledge of so-called pure poliomyelitic form of amyotrophic lateral sclerosis.) M. Bassi. 341.
Alcune Particolarita della Vascolarizzazione dell'-Ipofisi Studiate col Metodo Pickworth. (Some particulars of the vascularization of the hypophysis studied by the method of Pickworth.) C. Fazio and A. Carpaneto. 391.
*Il Peso Specifica del Liquor. Sue Variazioni Normali e Patologiche. (The specific gravity of the cerebrospinal fluid, its normal and pathological variations.) F. Addarii. 406.
*Contributo alla Conoscenza delle Sindromi Neurologiche da Infezione Parotitica. (Contribution to the knowledge of the neurological syndrome from parotid infection.) P. Ottonello. 413.
Poliradicoioneurite in Epidema di Poliomielite Anteriore Acuta. (Poluradiculoneuritis in an epidemic of acute anterior poliomyelitis.) P. Ottonello. 430.
Considerazioni Istopatologiche sopra Due Casi di Paralisi Ascendente Poliomielitica Tipo Landry. (Histopathological considerations of two cases of Landry's paralysis of ascending poliomyelitic type.) A. Grassi. 459.
Sulle Alterazioni Istologiche del Sistema Nervoso Centrale in Animali Sottoposti alla Crisi Insulinica Secondo il Metodo di Sakel. (On the histological alterations of the central nervous system in animals subjected to insulin crises according to Sakel's method.) L. Roizin. 491.
Le Psicosi Tabetiche. (Tabetic psychoses.) E. Medea. 532.

Poliomyelitic Form of A.L.S.—In a man of 31 a progressive condition developed with a fatal issue, and was characterized by muscular atrophy with flaccid paralysis starting in the lower limbs and spreading after some months to the upper limbs and trunk, and becoming complete in the parts first affected after about a year. Fascicular fibrillary contractions were observed in the root muscles of the limbs and in those of the hand. There were no cerebellar components, no loss of sensation, and no interference with pyramidal function while the patient was under observation. After a year an acute bulbar syndrome led to a dramatic termination. Histopathological examination showed a typical picture of amyotrophic lateral sclerosis. (R. G. G.)

Specific Gravity of C.S.F.—150 cases were studied. In the normal the average was 1,007 at a temperature of 4° C., and 0·999 at a temperature of 38° C. In pathological cases which showed a clear fluid there was no significant alteration from normal. In fluids which were turbid and which contained albumin or cells there was a slight increase of specific gravity. The test for the specific gravity of the c.s.f. is of little use in diagnosis. (R. G. G.)

Neurological Syndrome of Parotid Infection.—Parotid infection may be accompanied by meningeal symptoms and signs. More rarely signs of meningomyelitis and exceptionally encephalomyelitis are found. A case of encephalomyelitis occurring a fortnight after the parotitis is described. (R. G. G.)

SCHWEIZER ARCHIV FÜR NEUROLOGIE UND PSYCHIATRIE

Vol. 43. No. 2. 1939.

Untersuchungen über die Wirkung der Kurzwellen auf den Liquor cerebrospinalis. (Investigations on the effect of short-wave diathermy on the c.s.f.) W. Dürler. 209.

Kollaboration der Hirnforschung durch Standardisierung der Hilfsgeräte. (Co-operation in brain research by standardization of technique.) W. R. Hess. 221.

Anormalenzählung im Kanton Appenzell A.Rh. vom Jahre 1937. Bearbeitet im Auftrage der amtlichen Zählkommission. (Census of defectives in Canton Appenzell A.Rh. in 1937.) A. Koller. 225.

La Myéloarchitectonique Insulaire et l'Avant-Mur. (Myelo-architecture of insular and claustrum.) E. Landau. 287.

Beitrag zur Cardiazoltherapie der Schizophrenie nach v. Meduna (in Kombination mit der Schwefelfiebertherapie). (Cardiazol treatment of schizophrenia combined with sulphur fever treatment.) S. Novotny. 295.

Les neurodermatoses fonctionelles. (Functional neurodermatoses.) E. Ramel. 312.

Psychische Befunde bei einem Geschlecht mit myotoner Dystrophie. (Psychological study in a family with dystrophia myotonica.) J. F. Rittmeister. 329.

Normale und abwegige Entwicklung des zentralen Nervensystems im Lichte neuerer Amphibienexperimente. (Normal and abnormal developments in the central nervous system : experiments on amphibians.) G. Töndury. 360.

Relazione tra Differenziazione Strutturale e Funzionale dei Centri e delle Vie Nervose nell'Embrione di Pollo. (Structural differentiation and function of nervous centres and pathways in chick embryo.) F. Visintini and R. Levi-Montalcini. 381.

ZEITSCHRIFT FÜR DIE GESAMTE NEUROLOGIE UND PSYCHIATRIE

Vol. 165. March 1939.

This volume contains the contributions to the fourth annual meeting of the Association of German Neurologists and Psychiatrists held at Cologne, 25th–27th September, 1938.

Vol. 166. No. 1. March 1939.

Wilhelm Weygandt. B. Prinz. 1.

Chronische rheumatische Gehirnerkrankung als Ursache von Geisteskrankheiten. Eine klinisch-anatomische Studie. (Chronic rheumatic brain disease as a cause of mental disorder. A clinical and anatomical study.) W. L. Bruetsch. 4.

Katamnestische Untersuchungen über die Insulin-Shock-und Konvulsionstherapie der Schizophrenie. (Katamnestic researches in the treatment of schizophrenia by insulin shock and convulsion therapy.) T. Lehoczky, M. Eszenyi, B. Horányi-Hechst, and R. Bak. 24.

Eine Form von vorübergehendem jugendlichem adiposo-hypogenitalem Syndrom konstitutionellen Ursprunges. (A form of transitory juvenile adiposo-genital syndrome with a constitutional basis.) W. Dzierżyński. 81.

Elektrokardiographische Untersuchungen bei der Shock- und Krampfbehandlung der Schizophrenie. (Electrocardiographic studies in shock and convulsive treatment of schizophrenia.) D. Schmitt. 108.

Beitrag zur Kasuistik der Ganglioneurome des Kleinhirns. (Ganglioneuroma of the cerebellum.) H. Heinlein and Falkenberg. 128.

Über Veränderungen der Insulintoleranz und des Körpergewichts im Verlaufe der Insulinshockbehandlung Schizophrener. (Changes in insulin tolerance and body weight in the course of treatment of schizophrenia by insulin shock.) P. Plattner. 136.

Vol. 166. No. 2. April 1939.

*Eine chemische Untersuchung der Hirnschwellung. (A chemical investigation into brain swelling.) C. Riebeling. 149.

*Über den Trockensubstanzgehalt verschiedener Hirnteile. (The dry content of various parts of the brain.) T. Strobel. 161.

Über Eiweissschwellung der Leber bei Psychosen. (Albuminous swelling of the liver in psychoses.) C. Riebeling. 170.

Beitrag zur Klinik und Histopathologie der juvenilen Paralyse. (A contribution on the clinical and histopathological aspects of juvenile paresis.) F. Tebelis. 178.

Amnesie nach Trauma capitis. (Amnesia after head injury.) A. Verjaal. 221.

Studien über den Kohlehydratstoffwechsel bei Dystrophia musculorum progressiva. (Studies in carbohydrate metabolism in progressive muscular dystrophy.) D. Pallikan. 236.

Die Rolle des Isolierungsvorgangs bei der Zwangsneurose. (The role of isolation processes in compulsion neuroses.) N. Praeger. 251.

Vierter Beitrag nach der genetischen Bedingtheit der Homosexualität. (Fourth contribution on the genetic theory of homosexuality.) T. Lang. 255.

Aberglaube und Verbrechen (Zugleich ein Beitrag zur Frage der psychischen Induktion). (Superstition and crime. A contribution to the question of psychical induction.) F. Knigge. 271.

Die Methodik der lokalisierten Ableitungen hirnbioelektrischer Erscheinungen von der Kopfschwarte des Menschen, ihre Begrundung und Begrenzung. (The method of localized leads for bio-electric phenomena from the human scalp, their foundation and limits.) A. E. Kornmüller, and R. Janzen. 287.

Chemical Investigation in Brain Swelling.—The protein nitrogen was studied in various parts of the brain and correlated with wet and dry weights. In brain swelling there is not an intracellular œdema, but an increase of albuminous substance in the tissues which is shown by an increase in the dry weight and diminution of water content. In brain œdema there is an intercellular water increase. As œdema and swelling may be coincident, an estimation of dry weight alone is not sufficient for a diagnosis of brain swelling, but a quantitative protein nitrogen estimation is necessary. (G. M. G.)

Dry Content of Brain.—Various parts of the brain in various conditions in about 65 cases were dried for 14 days and weighed. In senile brains an increase of water content was found. An increase in dry substance weight was found in brain tumour with pressure, in toxic states, and in catatonic states and hyperkinetic states, and may be associated with the anatomical diagnosis of brain swelling. (G. M. G.)

Vol. 166. No. 3. May 1939.

Konrad Rieger. R. Gaupp. 309.
Beiträge zur Histopathologie präseniler und seniler Gewebsveränderungen des Zentralnervensystems. I. Über die Strukturmöglichkeiten seniler Drusen und über die fallweise verschiedenen Verläufe "Drusiger Entartung" der grauen Hirnsubstanz. (Contributions on the histopathology of senile and presenile tissue changes in the central nervous system. I. The possible structure of senile plaques and the various scattered plaque-like degenerations of the grey substance.) H. Jacob. 313.
Über die dynamisch-strukturellen Bedingungen des primären Beziehungswahns. (The dynamic structural conditions of primary delusions of reference.) R. Bak. 342.
Neue psychiatrisch-genealogische Untersuchungen an Hilfsschulzwillingen und ihren Familien. I. Die Zwillingsprobanden und ihre Partner. (A new psychiatic and genealogical investigation of twins in special schools and their families. I. The twin and his partner.) A. Juda. 365.
Der Okkultismus, seine Grundlagen und Gefahren. (Occultism, its basis and dangers.) W. Weygandt. 453.

ZENTRALATT FÜR NEUROCHIRURGIE

Vol. 4. No. 3. July 1939.

*Die Epidermoide des Rückenmarkes. Analyse eines Falles, zugleich Beitrag zur Frage der Entstehung der aseptischen Meningitis nach Epidermoidoperationen. (Epidermoids of the spinal cord. Analysis of a case and contribution to the question of the origin of aseptic meningitis after operations on epidermoids.) H. Verbiest. 129.
*Missbildungstumoren des Grosshirns. (Malformation tumours of the cerebrum.) W. Schär and E. Christensen. 142.
*Ein Pinealom mit diffuser Metastasierung in die Meningen. (A pinealoma with diffuse meningeal metastases.) T. Werner. 155.
*Über den durch Gefässprozesse bedingten Verschluss der Art. carotis interna. (Occlusion of the internal carotid artery by vascular processes.) W. Sorgo. 161.
Zum Problem der Commotio cerebri. (The problem of cerebral concussion.) E. Bay. 180.
Haltungsanomalien des Kopfes bei Hirntumoren. (Positional anomalies of the head in patients with cerebral tumours.) H. Sprockoff. 185.

Epidermoids of Spinal Cord.—One epidermoid is described which involves the spinal cord from L2 to the conus. The histogenesis of these tumours is discussed. The author believes that post-operative aseptic meningitis following removal of these tumours is due to the free fatty acid which is present in epidermoids. Animal experiments support this view. (J. S.)

Malformation Tumours of Cerebrum.—Five tumours are described in which the clinical course and histological structure justify the formation of a special group for these growths. They appear to be benign tumours. (J. S.)

Pinealoma with Diffuse Meningeal Metastases.—A patient aged 33 died in hospital with signs of a space occupying intracranial lesion without showing any localizing signs. Histological examination revealed that the pineal gland had undergone blasphomatous change and by spreading infiltration had involved the meninges in a diffuse manner. (J. S.)

Occlusion of Internal Carotid Artery.—Occlusion of the internal carotid may be due to arteriosclerosis, other types of vascular disease, or trauma. Hemiplegia of varying severity is the outstanding clinical sign. Arteriography is essential in order to establish the diagnosis. Twenty-one such cases have so far been described. (J. S.)

Vol. 4. No. 4. August 1939.

*Thyrogene intrarhachideale Geschwülste. (Thyrogenous intraspinal tumours.) O. Foerster. 198.
*Zur Frage der operativen Behandlung der Arachnitis spinalis. (The problem of surgical treatment of spinal arachnitis.) A. Stender. 214.
Die perkutane Arteriographie der Gehirngefasse. (Arteriography of the cerebral vessels by percutaneous puncture.) H. Wolff and G. Schaltenbrand. 233.
*Die Behandlung der posttraumatischen Spätepilepsie. (The treatment of post-traumatic late epilepsy.) W. Tönnis. 240.
Das Arteriogramm des pulsierenden Exophthalmus. (The arteriogram of pulsating exophthalmos.) H. Wolff and B. Schmid. 241.
Über die geschichtliche Entwicklung und den heutigen Stand der Klassifikation der Hirngeschwülste. (Historical evolution and present-day position of the classification of cerebral tumours—with special reference to gliomas.) K. J. Zülch. 251.

Thyrogenous Intraspinal Tumours.—Three cases are reported. One was practically cured by operation and subsequent X-ray therapy. A second case died soon after operation; whilst the third lived for four years. At necropsy no primary thyroid tumour could be found, although the tissue removed from the spine histologically was of thyroid origin. It was therefore assumed

that this tumour originated in an accessory thoracic thyroid. These tumours spread to the spine by continuity. (J. S.)

Surgical Treatment of Spinal Arachnitis.—Six cases of spinal arachnitis were treated surgically with complete cure in two cases. The other four were improved. In three cases abnormalities of the bone were found and considered to have been the cause. (J. S.)

Treatment of Post-Traumatic Late Epilepsy.—After surgical removal of the scar 87 per cent. of patients were found to have been free from fits 2–6 years after the operation. (J. S.)

Vol. 4. No. 5. August 1939.

*Intrakranielle Ganglienzellgeschwülste. (Intracranial ganglion cell tumours.) W. Tönnis and K. J. Zülch. 273.
*Experimentelle Untersuchungen über die Wirkung des Halssympaticus auf die bioelektrische Spannungsproduktion der Hirnrinde. (Experimental investigations on the influence of the cervical sympathetic on the production of bioelectrical tension by the cerebral cortex.) A. Asenjo. 307.
*Das Arteriogramm des pulsierenden Exophthalmus. (The arteriogram of pulsating exophthalmos.) H. Wolff and B. Schmid. 310.
Haltungsanomalien des Kopfes bei Hirntumoren. (Positional anomalies of the head in patients with cerebral tumour.) H. Sprockhoff. 319.
Über die geschlichtliche Entwicklung und den heutigen Stand der Klassifikation der Hirngeschwülste. (Historical evolution and present-day position of the classification of cerebral tumours.) K. J. Zülch. 325.

Ganglion Cell Tumours.—Ten cases of this type have occurred in the experience of the authors. Brain stem was affected in five of these cases. Those with the tumour in the cerebral hemispheres appear to constitute a group giving rise to symptoms in early youth and running a benign course for several years. Growths were nodular, affecting chiefly the lepto-meninges and forming cysts. Histologically they consisted chiefly of mature ganglion cells. (J. S.)

Cervical Sympathetic and Cerebral Cortex.—Interruption of the cervical sympathetic appears to decrease the bioelectrical potentials of the homolateral cortex. (J. S.)

Arteriogram of Pulsating Exophthalmos.—Passage of blood through the cavernous sinus in the case of a pulsating exophthalmos was traced anatomically and in one of three cases described by the authors a communication from the basilar sinus to the basilar vein of Rosenphal was observed. Treatment advised was ligature of the external carotid and if necessary of the superior thyroid artery. (J. S.)

BOOK REVIEWS

THE MECHANISM OF THOUGHT, IMAGERY AND HALLUCINATION

J. Rosett

(Columbia University Press, New York. Oxford University Press, London. 1939. Pp. 289. 15*s*.)

In this volume Dr. Rosett has brought to bear upon a consideration of the mental phenomena he names in the title the facts he considers pertinent elicited in the fields of experimental anatomy, physiology, pharmacology, and clinical neurology. Since the book is intended not only for medical men but also for all other intelligent people, he devotes the first half of the book to a lucid exposition of these facts. The well-trained neurologist will be familiar with all of this material and need read only the brief summary at the end of each of the chapters from II to VIII to see what evidence is to be used in the subsequent presentation. In the latter half of the book the author expounds his thesis, adding data obtained by introspection from himself and his patients. His explanations rest upon the theory that there is a " release of the essential function of a link in the nerve pathway when the activity of the link which precedes it in the direction of nerve conduction has ceased." For example, when a sensory receptive area of the cerebral cortex is destroyed, the recall of past experiences in the form of hallucinations in which the lost sensation plays a prominent part is due to an activation of the nerve systems extending away from the destroyed area—the association systems. The current assumption that an injury of a sensory area of the cerebrum produces hallucinations by irritating the connecting association systems is considered invalid by Dr. Rosett, since hallucinations and imagery occur in the state of attention and in the onset and termination of sleep. He ignores much contradictory evidence in his argument, such as the findings of Penfield upon cortical stimulation. Much more objective evidence is needed before his " theory of release " can be considered proven. The last half of the book deserves to be read by all investigators of the nervous system, as a result of whose subsequent work his notions will be either upheld or refuted.

THE SURGERY OF PAIN

René Leriche. Translated by Archibald Young

(Baillière, Tindall and Cox, London. 1939. Pp. 496. 21*s*.)

This extraordinary volume is devoted mainly to a discussion of the experiences of the author and his immediate pupils, and the presentation of a rationale for the procedures carried out. The viewpoints expressed constitute a departure from widely held opinion on many problems, hence the complete omission of any bibliographic reference to a single one of the papers mentioned is a gross defect. Leriche states that he has had to adopt a fresh outlook in many fields, " as though no previous work had been done in them." From such definitions as " axone reflexes, having their place of origin in the cutaneous nerve-fibres of the affected region, and their point of reflection in the cord " one gathers that his outlook has not been hampered by a maximum of knowledge of neurophysiology. He is willing to draw sweeping conclusions on such evidence as this. In one case of a decalcifying metastatic lesion of a low thoracic vertebra with severe pains he placed a solid tibial graft alongside the spinous processes, had the patient got up after 8 days, although he agreed that a lengthy immobilization would be required if the graft were to take. However, the

patient was relieved of pain, so on the basis of this one case he recommended this procedure " for the pains of metastatic spinal cancer with threatened or actual Pott's curvature." The author's style is strikingly verbose and repetitious, but the translator has made smooth reading in English of the material. Despite these acid criticisms a condemnation of the whole book is not intended. Every one of the chapters from V to XVIII contains records of difficult cases with long post-operative following periods in which forms of treatment originated by the author have been successful. Painful nerve injuries, causalgia, painful amputation stumps, Raynaud's disease, thrombo-angeitis obliterans, arteriosclerosis, painful scars, angina pectoris, and painful abdomino-pelvic malignant tumours are the principal subjects treated. Since orthodox English methods of treatment are unsatisfactory in many cases in these groups, those concerned with the advancement of therapeutic methods here will do well to evaluate the suggestions of Leriche by personal experience with his methods. His evangelistic style of presentation should lead to an unusually careful criticism rather than a brushing aside of his recommendations.

THE STUDY OF SOCIETY

Edited by F. C. Bartlett, M. Ginsberg, E. J. Lindgren, and R. H. Thouless

(Kegan Paul, Trench, Trubner, and Co., Ltd. 1939. Pp. 498. 10*s* 6*d*.)

With the initial aim of presenting to investigators in the social sciences an adequate survey of methods and problems of research, a representative group of psychologists, social anthropologists, and sociologists have joined in a remarkable team effort. Over the last few years twenty-three have met to discuss and revise the individual contributions on available methods in the related sciences. The resulting volume as we have it now is therefore a presentation of current views on which there is a fairly general agreement. Notwithstanding, very individual viewpoints obtrude. Thus the reader is told that " at the moment a knowledge of clinical psychiatry has no value for the social psychologist," social psychology having as its province phenomena that depend on group activity for their appearance, and the psychiatric contributions on the discontents of civilization go unmentioned. However, exceptions such as this contrast with the general soundness of the volume and the medical reader, always a potential sociologist, will find much of gain in these sketches of progress to-day in anthropology and psychology. As a guide to further reading it should prove suggestive. We look forward keenly to further work by this group.

THE POST-NATAL DEVELOPMENT OF THE HUMAN CEREBRAL CORTEX
VOL. I. The Cortex of the New-Born

J. le Roy Conel

(Harvard University Press, Cambridge, Mass. Oxford University Press, London. 1939. Pp. 114. 35*s*.)

As its name implies, this is the first volume of a projected monograph which, if continued in this manner, will be monumental. The author has surveyed the state of development at the time of birth in each of von Economo's cortical areas and has studied Nissl, Weigert, Cajal, and Golgi Cox sections of each. The size of the nerve cells and their number per unit of area are estimated for each cortical layer and the arrangement and state of myelination of the fibres are also described. The results of the measurements of the iso-cortex are summarized in a useful table. This part of the book occupies more than 100 quarto pages. The second half of the book consists of ninety-eight plates, most of which contain two large photomicrographs

or drawings. These figures give some idea of the scope of the work, which appears to be a very careful and complete study.

The only thing lacking appears to be reference to the state of differentiation of the neurons. To some extent this may be obtained from the measurements of cell size, but it would also be useful to know the ratio of cell size to nuclear size in the different layers of the cortex at various stages of development. Bok has shown that this ratio is fairly stable in the mature nerve cell, but the adult ratio must be attained gradually and its value at any age might be a valuable index of the stage of development of the neurons.

STUDIES OF THE MORPHOGENESIS OF THE BRAIN IN REPTILES

K. H. Krabbe

(E. Munksgaard, Copenhagen. 1939.)

This monograph is composed of detailed descriptions of the external appearance of the brain in various stages of development in five different reptilian species. To this is added a rough account of the cellular distribution in the forebrains and midbrains of the same five species as seen in microscopic cross sections. Three or four different stages from each of the five species are so described. *Gongylus scellatus*, *Chamælo bitæniatus*, *Chelydra serpentina*, *Alligator Mississippensis*, and *Tropidonotus natrix* are the five forms selected. To facilitate precise observation of the external morphology each specimen described was cut in serial section. Camera lucida drawings at a magnification of 50 or 100 diameters were then made of the outlines of each section and wax plates corresponding to the drawings were joined together to form a reconstruction of each brain. Excellent drawings of three views of each reconstruction are included in the illustrations, and there are also microphotographs of many of the cross-sections described. Although there are comparisons of the same structure in the various species scattered through the text, there has been no attempt to summarize or tabulate the principal features or differences in the various stages and species. Consequently, even though the work is of value to the scholar in pure embryology, the research worker interested in correlating structure with function will find that the textual matter requires long, tedious study for a satisfactory grasp of the material.

THE SCHIZOPHRENIFORM STATES. A KATAMNESTIC STUDY BASED ON INDIVIDUAL RE-EXAMINATIONS

Gabriel Langfeldt

(E. Munksgaard, Copenhagen ; Humphrey Milford, London. 1939. Pp. 134.)

The book is essentially a sequel to an earlier work (1937) on typical schizophrenic conditions. In this latter volume the author takes 100 cases which were diagnosed " schizophrenia ? " at the Oslo Psychiatric Clinic. As a result of re-examination of these cases he concludes that they should be divided into two main groups : first, a group with a bad prognosis, which should in the first place have been called " typical process schizophrenia " ; secondly, a heterogeneous group of schizophreniform psychoses with a good prognosis. He feels that from this latter group many of the " cures " with insulin and cardiozol therefore have come.

There are many potential dangers and fallacies in this type of argument based as it is on a retrospective diagnosis. There are also many who would find difficulty in accepting his sharp distinction between the endogenous " process schizophrenias " on the one hand and the more reactive schizophreniform states on the other.

Nevertheless he presents his arguments convincingly and well, and one hopes that he will now proceed to undertake a statistical survey of the development of a series of cases in which he has established his differential diagnosis at the time of the patient's admission to hospital.

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Brown, A.B. (1845). *Rev. Neurol.*, 169, 427.

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